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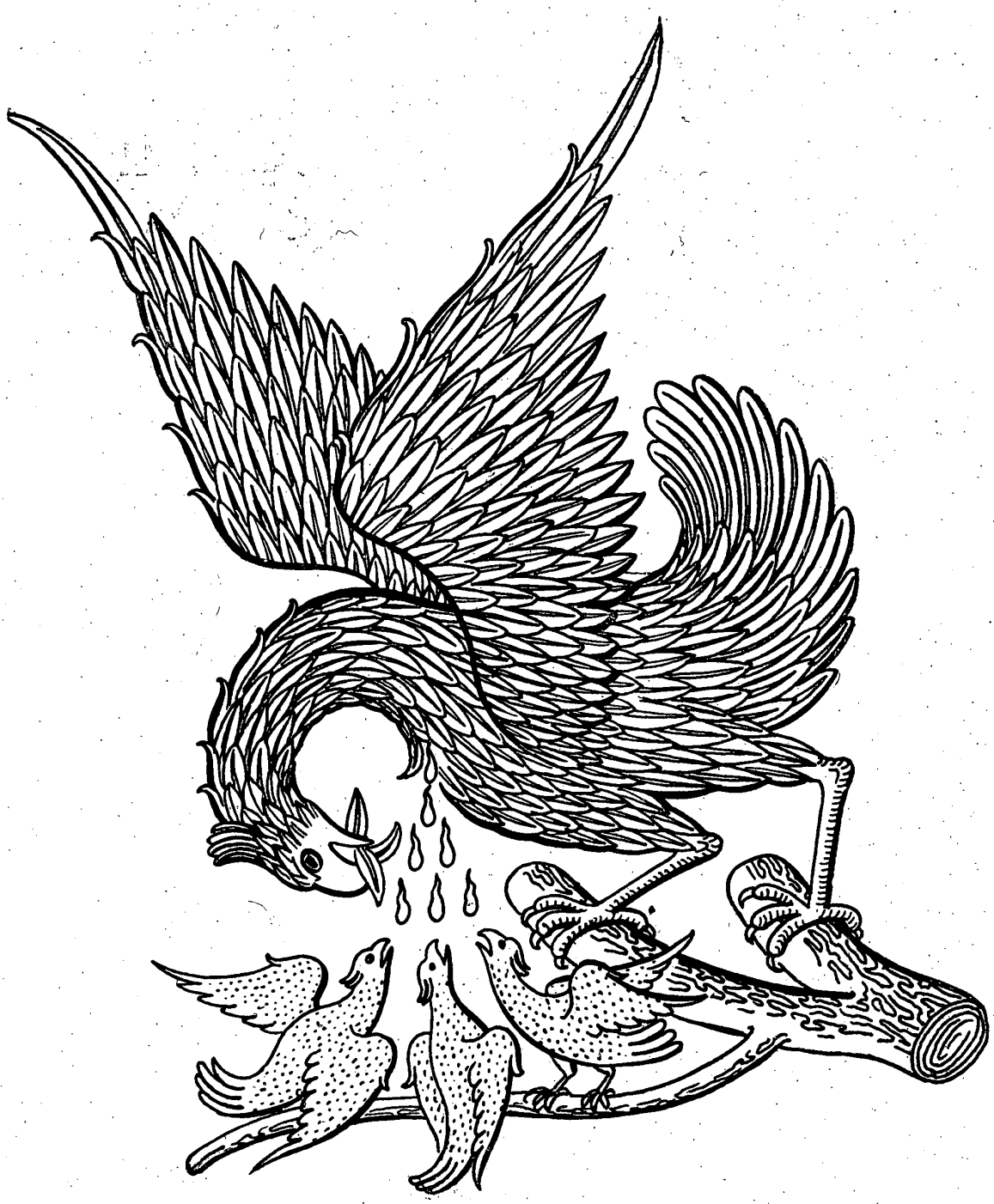

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THE COAGULOGRAM
AN AID IN THE EVALUATION OF DISORDERS IN BLOOD CLOTTING

Prof. M, GERENDÁS

I—The Role of Blood Clotting in the Arrest of Haemorrhage

The coagulation of extravasated blood is one of the important processes in natural haemostasis. *The fibrin network produced in the course of coagulation seals the aperture in blood vessels* and thus contributes to the arrest of bleeding.

This process involves two opposite requirements. Circulating blood must remain fluid all through life, while at sites of damage blood clotting should proceed at a rapid rate. A complicated mechanism serves to meet both demands.

As long as blood clotting is normal, no thrombi are formed within the blood vessels, and the blood leaving the vessels at any site of damage will clot within three to four minutes, coagulation being the most important phase in the arrest of bleeding.

However, *when blood clotting is irregular, the process of coagulation may deviate from normal in either direction.*

A decrease in thrombin production or an increase in the amount of thrombin inhibitors affects coagulation, therefore haemorrhages may ensue. On the other hand, an accumulation of agents promoting the production and action of thrombin, or a decrease in antithrombins enhances coagulability and consequently thrombosis may develop. Nor is coagulability of blood the only factor responsible for haemorrhagic or thrombotic processes. Apart from the process of coagulation taking place in plasma, other factors, which may be termed "non-plasmatic factors", also play their part in the development of pathological conditions.

By interaction of above factors, haemostasis takes place in four phases: contraction of injured vessels, agglutination of thrombocytes, the phase of blood clotting, and, finally, retraction of the clot. These phases are closely connected and may mutually compensate one another for any deficiency, but irregular blood clotting cannot be satisfactorily counterbalanced by any of the other phases (1). Moreover, plasmatic and non-plasmatic factors are often involved simultaneously in pathological conditions.

In haemostasis the importance of blood clotting is obvious, yet for a long time its role in thrombus formation was disregarded, the common methods of staining fibrin having failed to demonstrate fibrin among the thrombocytes within the primary nucleus of postoperative thrombi. Recent investigations, especially electronmicrophotograms, have proved the presence of fibrin in such nuclei (2). By this evidence it has been confirmed that the appearance of fibrin is also responsible for thrombus formation. Further proof in support of this view is that anticoagulants, e. g. heparin, may be used with success for the prevention or arrest of thrombosis.

It clearly follows that *increased or decreased coagulability may play roles of equal importance in the various disorders of blood clotting.*

II—Factors of the Coagulation Process

According to Schmidt-Moravitz's classical theory on the mechanism of blood clotting, the process involves four factors: fibrinogen (factor I), prothrombin (factor II), thrombokinase (factor III), and ionised calcium (factor IV). These substances are produced in different organs (fig. 1), hence pathologic changes in the latter may exert an influence on blood coagulation. Recent investigations have corroborated the existence of other factors, but their site of production is still unknown.

We do not intend to discuss in detail the development of theories on blood clotting or the present aspects of the problem (3, 4). In the following we present an analysis of the factors and processes whose role has been clarified and found to be important for our investigations.

The first step in clotting is known to be a release of tissuekinase from damaged tissues, and of thrombokinase (thromboplastin) from platelets disintegrated by contact with the damaged area of the vascular wall. In the presence of these kinases, Ca ions, and the so-called clot-accelerating factors (factor V and VI, Owren's factor, factor VII, Koller's factor), part of the prothrombin is converted into thrombin.

If this were the only way of thrombin production it would be insufficient. Thrombin has been shown to increase the rate of activation of thrombokinase and of clot-accelerators, thereby producing new quantities of thrombin. Thus thrombin promotes its own production, i. e. it develops by way of autocatalysis. Factor VIII (antihaemophilic globulin), factor IX (of Christmas) as well as factor X have been found to participate in the process. *The number of factors known to be involved in the mechanism of coagulation has therefore risen to ten.*

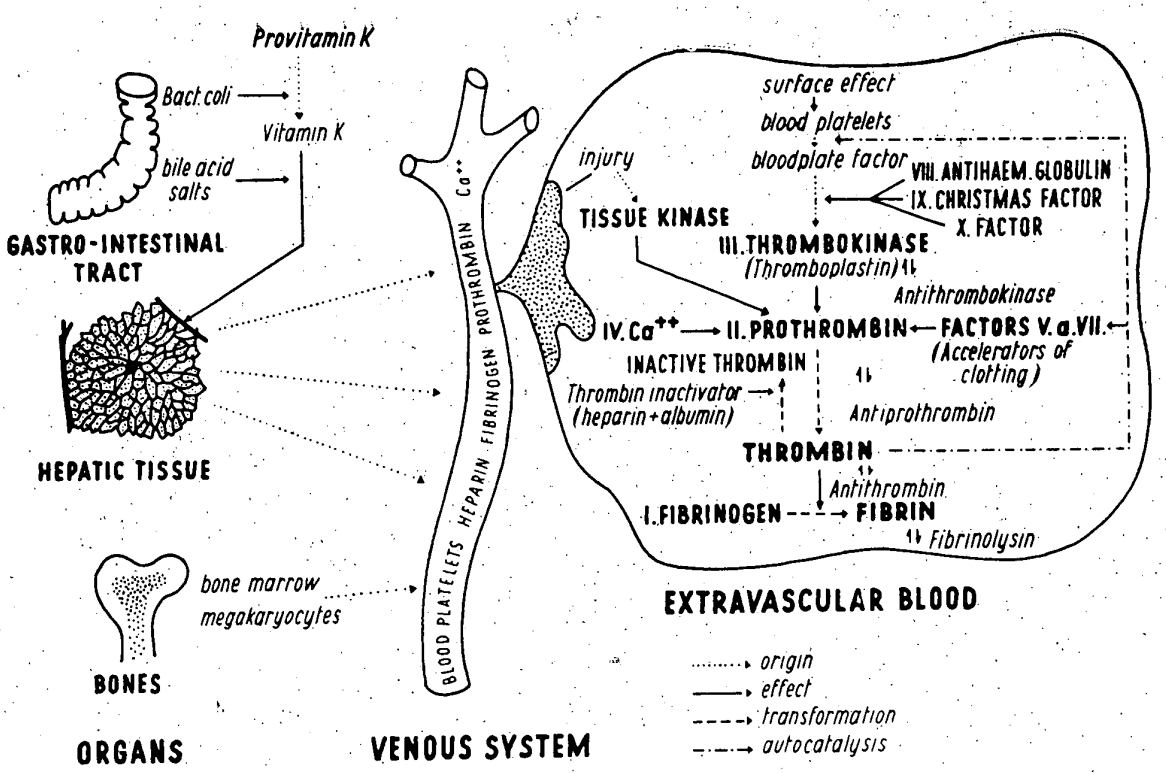


Fig. 1—Schematic representation of the process of coagulation

The role of anticoagulant agents should also be taken into consideration. For example, antithrombokinase counteracts thrombokinase, antiprothrombin is a counter-agent to prothrombin, while simultaneously with the production of thrombin its inactivation has also been noted. In the latter process heparin and an albuminlike plasma protein inactivate thrombin by an enzymatic action (5). Apart from this process, the effect of some "non-heparin" antithrombin is also demonstrable. The fibrin formed is broken down by fibrinolysin.

The scheme of coagulation described by Schmidt-Moravitz has thus to be supplemented by *three statements of essential importance:*

1. In addition to calcium and kinase, accelerating factors (factor V and VII) are also required for the conversion of prothrombin.

2. An *autocatalytic process* is responsible for the production of thrombin in sufficient quantities.

3. Inhibitory actions (mainly the inactivation of thrombin) in conjunction with thrombin production by way of a dynamic equilibrium interact to provide the thrombin level required for undisturbed clotting; hence any change in the quantity of inhibitory substances is just as likely to lead to disorders of clotting as does increased or decreased thrombin production.

III—Disturbances in the Process of Coagulation

Coagulation of blood may be disturbed in two ways (fig. 2): by a tendency to haemorrhages, or a tendency to thrombosis. Non-plasmatic factors may also be involved in either of these conditions. In fig. 2 these factors are separated by a broken line from true coagulation factors, indicating that they are outside the scope of the present paper.

Our classification was intended to present *a review of the coagulative action of the factors that are amenable to demonstration by laboratory methods.* In so doing we have deviated from the classification by Koller (6) and, regardless of pathogenesis, comparison is based on *changes in the quantity or activity of coagulant and anticoagulant factors.*

As seen in fig. 2, a marked mirror image tendency is detectable in the outlines of the two groups. Our studies have furnished evidence showing that factors that increase in certain pathological conditions may decrease or be absent in others. For example, certain types of thrombosis are associated with an increase of prothrombin or an accelerated rate of autocatalysis, etc. whose absence is a familiar feature in haemorrhagic diseases. This finding justifies the mirror image confrontation of groups, and makes it possible to discuss disorders in clotting from a uniform point of view.

IV—The Importance in Therapy of Studies Concerned with Coagulation Factors

Since deficient production and activity of coagulation factors are just as frequent causes of irregular blood clotting as are excessive production or hyperactivity, detailed studies of these factors are essential for diagnosis and effective therapy. So-called "complex" tests have already been adopted by numerous laboratories (7, 8, 9).

In this country Horn, Kovács, and Altmann in 1950 introduced a method (10) involving the determination of values for eight to ten factors. These authors tabulate their data in a form they term "coagulogram" and the origin of the disorder in clot-

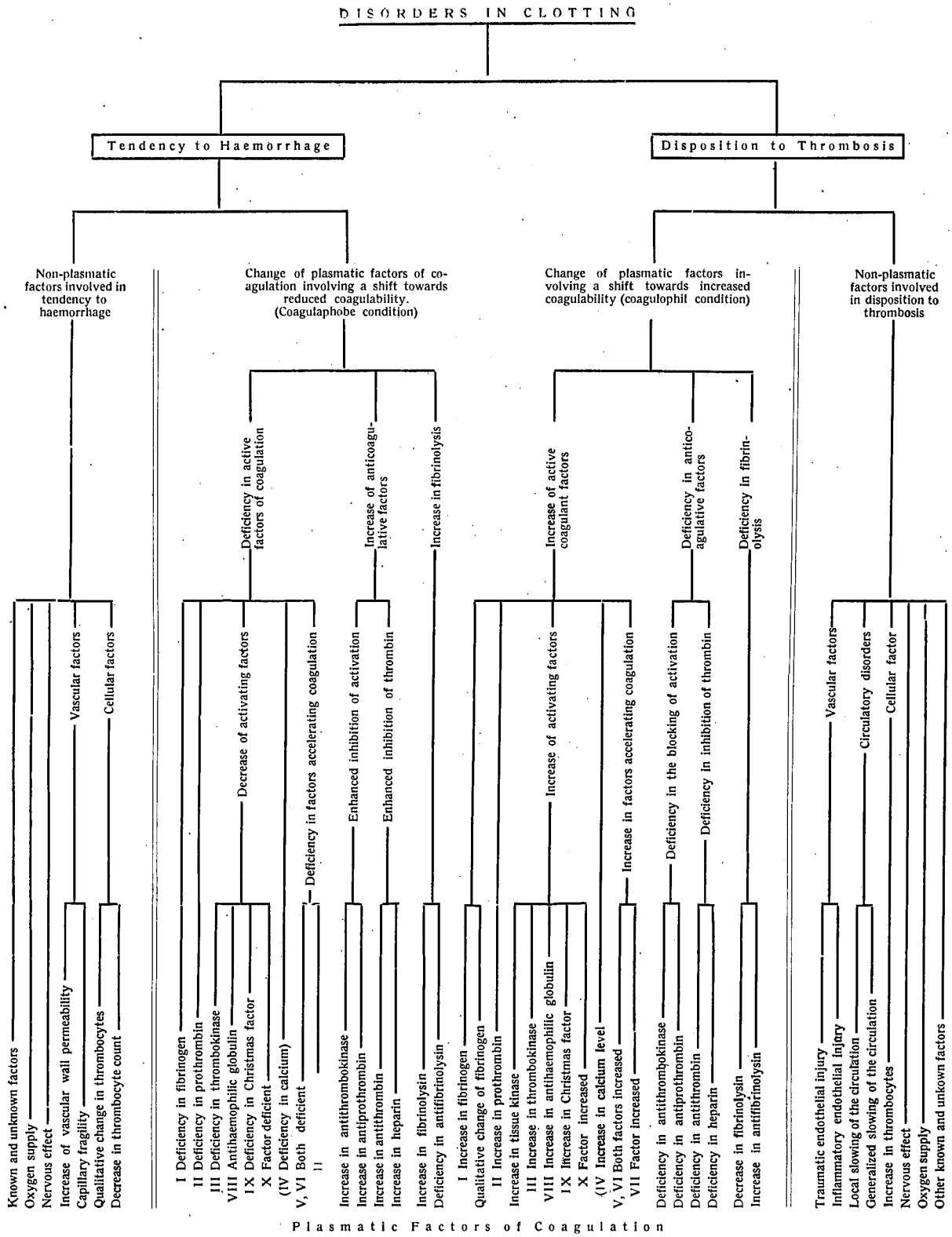


FIG. 2—FACTORS INVOLVED IN THE DISORDERS OF COAGULATION

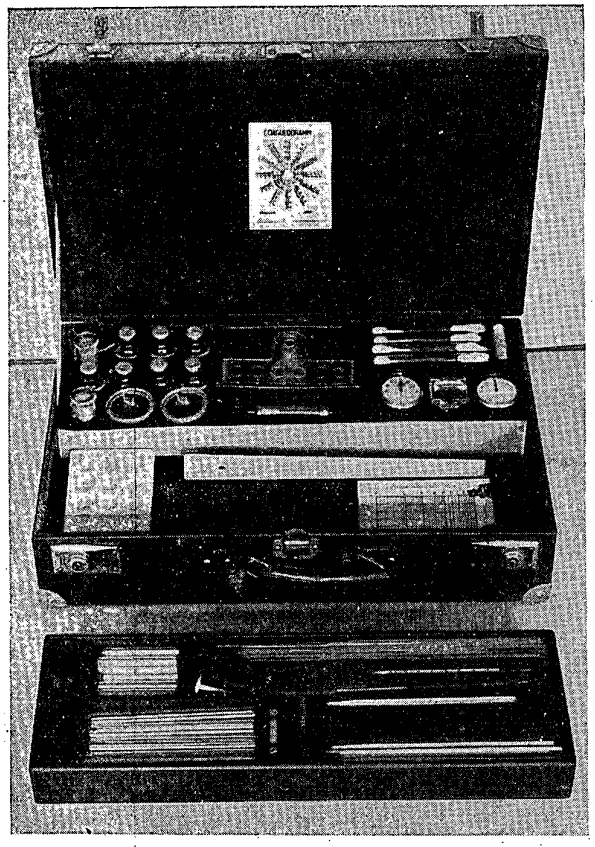


Fig. 3—Ready for use kit, containing the solutions and equipment required for plotting the coagulogram

ting is determined by a comparative analysis of all the data. Procedures of this type are very helpful in differential diagnosis of disturbances in blood clotting (11, 12, 13).

However, tabulated data are not easy to work with. The determination of deviation from normal values and the recognition of correlations are time-consuming tasks for the busy practitioner. We have therefore introduced a method of graphic (illustrative) presentation more suitable for clinical use.

V—Graphic Method (Graphic Coagulogram) for the Evaluation of Disorders in Clotting

In the literature of recent years tests for the determination of 15 to 20 factors of coagulation have been described as relevant in the diagnosis of disorders of coagulation. While developing our method we carefully selected the experiments most characteristic for identifying any one pathological condition. At present our coagulogram is determined on the basis of tests for twelve factors. The methods are partly those known from the literature, partly they have been worked out by ourselves. Care was taken to use tests whose technique requires simple laboratory equipment. The ready for use kit is shown in fig. 3.

We have constructed a practicable diagram for the evaluation of data obtained by the coagulation tests (15). The scales for recording the data have been drawn up in the form of a star (fig. 4). The scales are divided to let the values for blood from the normal individual (normal values) fall on the perimeter of the dotted circle in the figure (fig. 5). Physiologic variations have been also considered and allowance for them has been made by plotting alongside the circle limit values taken from the literature or determined by ourselves. When coagulability increases, i. e. coagulability of blood shifts toward the thrombotic direction, the points fall inside the circle (fig. 6); when coagulability decreases (a shift into the haemorrhagic direction), some results fall outside the circle (fig. 7). Thus at a glance the coagulogram immediately reveals whether we are faced with a tendency to thrombosis, to haemorrhagic diathesis, or with normal conditions.

Moreover, in some pathological conditions the deviation of values produces a characteristic alteration in the shape of the coagulogram. From the resulting polygonal patterns—and due consideration of the evidence obtained at the patient's bedside and the case history—conclusions can be drawn also as to the type of disease (haemophilia, hypoprothrombinaemia, etc.).

VI—Tests

For the construction of the coagulogram plasma and serum from the test subjects are required. Plasma and serum from a normal individual, taken simultaneously with the test samples, serve as controls.

The essential points in the determination of the twelve factors of coagulation are as follows:

(1) *Determination of Bleeding Time*

In the coagulogram the value of bleeding time furnishes information about vascular factors and the behaviour of thrombocytes, as well as about factors of coagulation. Protracted bleeding time in the presence of normal clotting time indicates that the disturbance in haemostasis is to be attributed to "non-plasmatic" factors (vascular walls, thrombocytes, etc.). Though the determination of bleeding time is a method lacking accuracy, it may be of aid in extreme cases.

For determining bleeding time we use Duke's method.

Normal values range from 100 to 180 seconds.

(2) *Clotting Time of Recalcified Plasma*

The value of clotting time applies to all the factors involved in coagulation. Clotting time alone, however, is non-contributory, since a deviation from normal affords no help in detecting the factor responsible for the disorder; on the other hand, normal values may occur notwithstanding disturbances in other factors. In such cases "normal" clotting is the result of a compensatory interaction. It is therefore expedient to investigate the other factors of haemostatic function by means of the coagulogram.

Recalcified plasma is used in the test which can thus be performed with the other tests in the laboratory.

The test is made in a china dish at room temperature and appearance of clot is determined by means of a glass hook.

Normal values for the onset of clotting in recalcified plasma range from 180 to 250 seconds.

(3) *Estimation of Prothrombin Level*

The prothrombin level is estimated in order to assess the amount of prothrombin available for thrombin production. The one-stage method of Quick is used for this test.

Values: Normal values range from 80 to 110%. Values in the range of 60 to 80% indicate a moderate decrease of prothrombin, while values below 60% stand for marked loss. Values higher than 110% indicate a pathological elevation of prothrombin level.

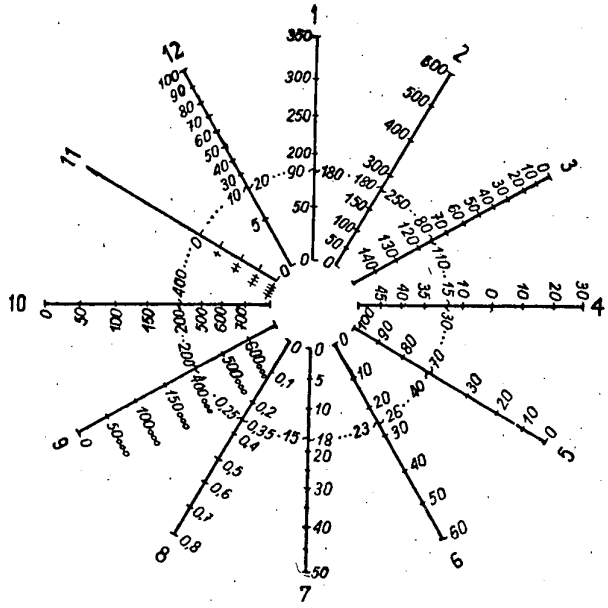


Fig. 4—Star shaped diagram for recording the results of tests for coagulation factors (coagulogram form)

LEGEND

1—Bleeding time (sec.)
2—Recalcified clotting time (sec.)
3—Prothrombin level (%)
4—Serum effect (%)
5—Prothrombin consumption (%)
6—Thrombin time (sec.)
7—Toluidine-blue time (sec.)
8—Thrombin inactivation (k)
9—Thrombocyte count
10—Fibrinogen content (mg %)
11—Fibrinogen B
12—Fibrinolysis (%)

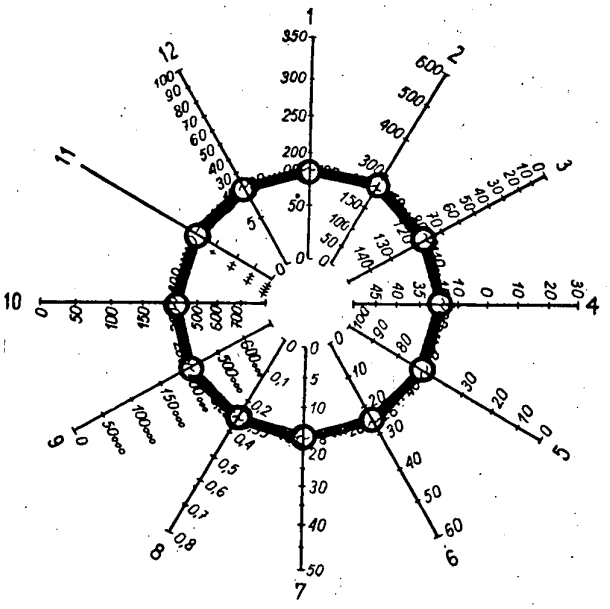


Fig. 5—The data for blood from a normal individual give a regular, circular diagram

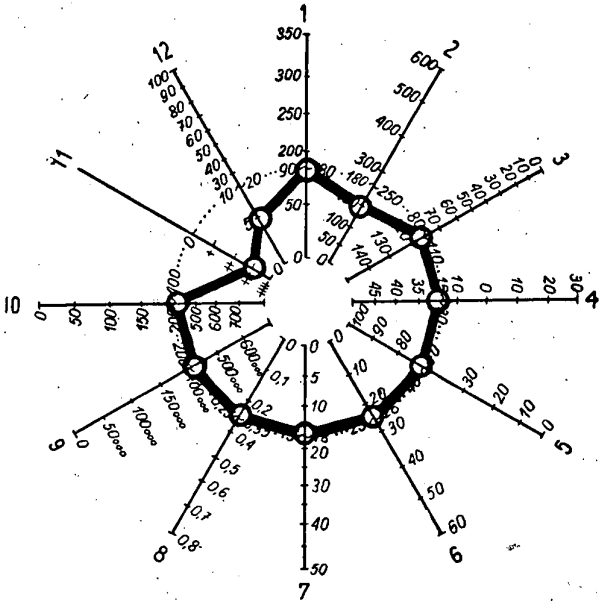


Fig. 6—In the presence of increased coagulability certain values fall within the circle

(4) *Test for Clot-Accelerating Factors in Serum*

The test measures the accelerating action of test serum on the prothrombin time of control blood from a normal individual. The action is brought about by the function of clot-accelerators in the serum (16), hence the information obtained relates to factors V and VII. The activity of serum is expressed in per cent. values.

Normal values: The serum of normal blood reduces prothrombin time by 15 to 20 per cent. Serum activity may be zero when the amount of clot-accelerators is reduced in the serum, or even negative values may occur in the presence of anticoagulants.

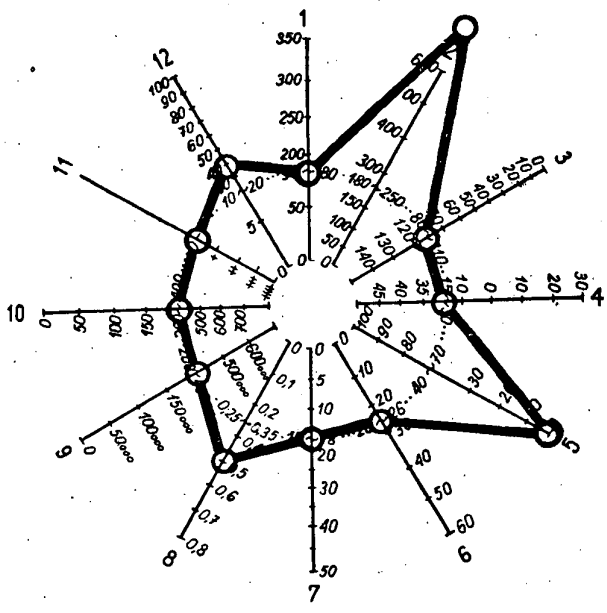


Fig. 7—In the presence of diminished coagulability certain values fall outside the circle

(5) *Estimation of Prothrombin Consumption*

Estimation refers to the amount and rate of utilization of prothrombin still present in the serum after coagulation has taken place. The values obtained supply information concerning the autocatalytic production of thrombin, i. e. the function of factors VIII and IX.

One hour after sampling the prothrombin still present in the serum is converted by kinase into thrombin which is then tested for activity. The same procedure is repeated three hours later. The decrease in thrombin during the interval between the two tests is expressed in per cent. value.

Values: Prothrombin consumption in normal serum, 40 to 70 per cent. In haemophilia, values are around 0, in the presence of a tendency to thrombosis they reach 90 to 100 per cent.

(6) *Determination of Thrombin Time*

The determination of thrombin time and toluidine-blue time serves to detect the presence of anticoagulants in plasma from the test subject. A prolongation of thrombin time suggests the presence of anticoagulants. If toluidine time, as determined by the method described in section (7), is normal, anticoagulant action is due to heparin ; if, however, toluidine-blue fails to shorten the prolonged thrombin time, an antithrombin dissimilar to heparin is likely to be present.

For the test we use a thrombin solution adjusted to 25 seconds clotting in normal plasma.

Normal values: Normal thrombin time is 25 seconds, with physiologic variations ranging from 23 to 26 seconds.

(7) *Thrombin Coagulation in the Presence of Toluidine-Blue*

Toluidine-blue binds heparin and thereby neutralizes its anticoagulant action. The dye thus shortens thrombin time, allowing conclusions to be drawn as to the free heparin content of plasma. A 0.1 per cent. solution of toluidine-blue is used in the test.

Normal values: In the presence of toluidine-blue normal coagulation time is 7 to 8 seconds shorter than thrombin time. A greater difference points to the presence of increased amounts of circulating heparin.

(8) *Determination of the Rate of Thrombin Inactivation*

Thrombin formed in the course of clotting soon disappears from the serum. For the determination of the rate of antithrombin action a thrombin solution of known activity is added to the test serum, which is then examined for clotting power at one minute intervals. The coagulation times so obtained are used for calculating the value of k for the rate of thrombin inactivation, either by mathematical computation or graphically (17).

Values: For k in normal blood, 0.25 to 0.35. In haemorrhagic disease k may range as high as 0.8 to 1.1, while in thrombotic conditions we have measured values as low as $k = 0.12$.

(9) *Determination of the Thrombocyte Count*

Determination of the thrombocyte count serves to reveal whether changes in the number of thrombocytes (cellular factor) play a role in the disorder of clotting.

The thrombocyte count is determined by the method of Fonio.

Morphology of the thrombocytes also requires attention. Polymorphism, polychromasia, etc. suggest functional disorder (thrombopathy). *Normally,* thrombocytes number 200,000 to 400,000 per cu. mm.

(10) *Estimation of Fibrinogen Content*

This test serves to reveal increase or decrease of fibrinogen.

The fibrinogen content of plasma is estimated by coagulation with thrombin ; the resulting fibrin is purified, dried, and weighed.

The weight of the dried fibrin clot is given in mg %.

The *value* of fibrinogen for normal plasma varies from 200 to 400 mg %.

(11) *Determination of Labile Fibrinogen*

Increased coagulability of blood is often due to qualitative changes in fibrinogen.

Labile fibrinogen (fibrinogen B) is determined according to Lyons. 2 per cent. beta-naphthol is used and the strength of the precipitate is indicated with crosses.

Labile fibrinogen does not occur in normal blood. Its presence suggests thrombosis, but it may occur also after excessive bleedings.

(12) *Test for Fibrinolysis*

The test measures the clot-lytic action of blood.

Essentially it is based on a quantitative determination of fibrin. Two samples are taken ; in one the clots that appear in the plasma are tested for quantity immediately after clotting, in the other 24 hours after clotting. From the two values we calculate the amount of fibrinogen lysed in 24 hours.

The fibrinolysis *value* for normal plasma varies from 10 to 20 per cent.

VII—Evaluation of Data

The values referring to single factors are put down on the blank form of the coagulogram and the resulting points are connected by lines. It is practicable to use a rubber stamp for putting down the scheme of the coagulogram in case histories.

Experience has shown that the coagulogram is a useful aid in the diagnosis of more commonly encountered pathologic conditions. Of course, single branches of the coagulogram may be further developed by examining also other factors or by replacing one test by an other. For example, when serum activity deviates from normal, complementary tests are to be carried out in order to decide whether the disorder is caused by factor V or factor VII. In haemophilia, tests against antihaemophilic globulin will help to differentiate between A and B type haemophilias (17).

The coagulogram may be further developed by including tests for heparin tolerance, for clot retraction, etc., or by the introduction of methods already practiced at the laboratory doing the tests. Micromethods may also be employed, especially in pediatric work. In such cases the scales of the coagulogram should be readjusted or additional scales drawn up, but care should be taken that the normal values for the new factors fall inside the circle in the centre and that the division of the scales be accurate. However, it is not expedient to increase the number of tests beyond a certain limit, because it may render investigation too laborious and evaluation too complicated.

The pathologic conditions that can be differentiated by means of the 12-pointed star-shaped coagulogram used by ourselves are reviewed in the following section.

VIII—Coagulograms for Common Disorders in Clotting

The first step in checking the reliability of our coagulogram was to give it a trial in clinical cases. Several hundreds of coagulograms were made in the period 1953—55 and an analysis of the compiled evidence has shown that the diagrams obtained in different pathological conditions or syndromes are of characteristic shape and easy to identify. These diagrams serve as type-coagulograms and facilitate diagnosis in subsequent cases. Type-coagulograms may of course be constructed also for conditions other than those described.

COAGULOGRAMS OF HAEMORRHAGIC CONDITIONS

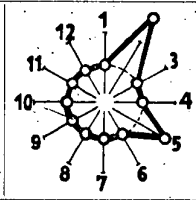
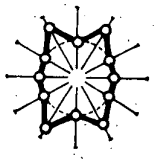
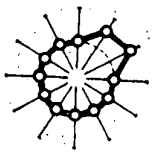
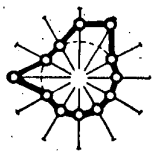
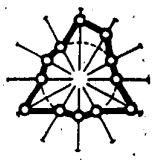
	Investigated factors	Haemophilia	Hyperheparinaemia	Hypo-prothrombinaemia	Fibrinopenia	Kinase deficiency due to thrombopenia
1	Bleeding time	normal	normal	normal	prolonged	prolonged
2	Recalcified clotting time	markedly prolonged	prolonged	prolonged	prolonged	slightly prolonged
3	Prothrombin level	normal	norma lor low	low	normal	normal
4	Serum effect	normal	normal	normal	normal	normal
5	Prothrombin consumption	markedly reduced	normal	normal	normal	reduced
6	Thrombin time	normal	markedly prolonged	normal	normal	normal
7	Toluidine blue	normal	normal	normal	normal	normal
8	Thrombin inactivation	normal	increased	normal	normal	normal
9	Thrombocyte count	normal	normal	normal	normal	markedly reduced
10	Fibrinogen	normal	normal	normal	markedly decreased	normal
11	Fibronogen B	∅	∅	∅	∅	∅
12	Fibronolysis	normal	normal or increased	normal	normal or increased	normal
	Coagulogram Types :					

FIG. 8—COAGULOGRAMS OF HAEMORRHAGIC CONDITIONS

(A) HAEMORRHAGIC CONDITIONS

Haemophilia is essentially a disorder in the autocatalytic genesis of thrombin. The values for prothrombin consumption will therefore show sharp peaks, falling mostly to point 0. The clotting time of plasma is considerably lengthened (fig. 8). This condition is frequently associated with an increased activation of thrombin and enhanced fibrinolysis (fig. 7).

Hyperheparinaemia. An increase of available heparin in the circulation is a relatively frequent condition. The increase may be spontaneous or may be the result of exposure to massive irradiation (ultraviolet, X-ray, or atomic).

The coagulogram will show extra-circular values in the first place for thrombin time and thrombin inactivation, as well as prolonged clotting time of recalcified plasma. Fibrinolysis values also often rise to peaks (fig. 8 ; hyperheparinaemia).

Hypoprothrombinaemia. This is the most often diagnosed haemorrhagic syndrome, caused by deficient prothrombin production of the liver.

COAGULOGRAMS OF THROMBOTIC CONDITIONS

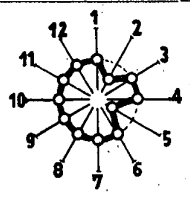
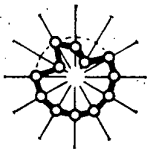
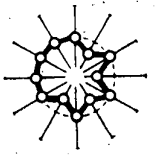
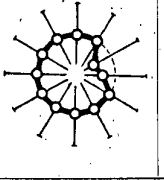
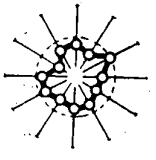
	Investigated factors	Hyperthrombo-plastinaemia	Fibrinogen lability	Hypoheparinaemia	Hyper-prothrombinaemia	Polygenic thrombosis
1	Bleeding time	normal	slightly shortened	normal	normal	shortened
2	Recalcified clotting time	shortened	shortened	shortened	normal	shortened
3	Prothrombin level	normal	normal	normal	markedly elevated	normal
4	Serum effect	normal or increased	normal	increased	slightly increased	increased
5	Prothrombin consumption	markedly increased	normal	normal	normal	increased
6	Thrombin time	normal	normal	shortened	normal	shortened
7	Toluidine blue time	normal	normal	normal	normal	shortened
8	Thrombin inactivation	normal	normal	low	normal	low
9	Thrombocyte count	normal	normal	normal	normal	high
10	Fibrinogen	normal	normal	normal	normal	high
11	Fibrinogen B	∅	+++	∅	∅	+++
12	Fibrinolysis	normal	normal or reduced	normal	normal	reduced
	Coagulogram Types:					

FIG. 9—COAGULOGRAMS OF THROMBOTIC CONDITIONS

In the coagulogram the values for clotting time of recalcified plasma and for prothrombin level will fall outside the circle (fig. 8; hyperprothrombinaemia). It is to be noted that a lengthening of prothrombin time as determined by Quick's method does not necessarily indicate a decrease in prothrombin level, since factors V and VII are also involved in the conversion of prothrombin. Lowered coagulogram values also for serum activity therefore indicate a deficiency in clot-accelerators rather than hypoprothrombinaemia.

Fibrinopenia. Fibrinopenia is a decrease or total absence of circulating fibrinogen. Values below 200 mg% are pathological, but haemorrhages tend to occur only at levels below 100 mg%.

The coagulogram shows lengthening of bleeding- and of recalcified plasma clotting-times and a very low level of fibrinogen (fig. 8 ; fibrinopenia). In case fibrinopenia is due to fibrinolysis, the fibrinolysis value will also fall outside the basic circle in the coagulogram.

Thrombokinase deficiency is a disorder due to a deficiency of thrombocytic factors.

The coagulogram shows prolonged bleeding- and recalcified plasma clotting-times and a diminution of prothrombin consumption. If also the thrombocyte count is low, the diagnosis is thrombopenia (fig. 8 ; kinase deficiency due to thrombopenia). On the other hand, structural changes in thrombocytes indicate that the condition belongs to the thrombopathies, and as such requires further differentiation by haemato-morphological methods.

(B) THROMBOTIC DISEASES

Hyperthromboplastinaemia is due to intensified autocatalytic thrombin production. The condition is caused by an increase in the level of thromboplastic agents (e. g. antihaemophilic globulin), hence it may be considered as the mirror image of the haemophilic disorder.

The coagulogram shows an excessive increase in prothrombin consumption. As a result the value for clotting time of recalcified plasma will also fall inside the circle. Serum activity is often increased (fig. 9 ; hyperthromboplastinaemia). According to our investigations, hyperthromboplastinaemia is one of the commonest causes of thrombotic disorders in clotting.

Fibrinogen lability. Fibrinogen is converted into fibrin in two steps. First fibrinogen is converted into a more coagulable form. Lyons has observed that labile fibrinogen may occur also in pathological conditions ; it produces a disorder in coagulation shifting towards thrombosis. The appearance of labile fibrinogen is usually associated with shortened bleeding- and clotting-times (fig. 9 ; fibrinogen lability).

Hypoheparinaemia. This condition is based on a diminution of the amount of circulating available heparin. The coagulogram shows a reduction in thrombin time, associated with a reduction of recalcification time, diminution of serum activity, and usually also of thrombin inactivation (fig. 9 ; hypoheparinaemia). The coagulogram pattern is the mirror image of that presented by hyperheparinaemia.

Hyperprothrombinaemia. The syndrome is due to intensified production of prothrombin.

The coagulogram shows a characteristic, remarkably high prothrombin level. The pattern is the mirror image of that seen in hypoprothrombinaemia. An increase in serum activity is also present (fig. 9 ; hyperprothrombinaemia).

Polygenic thrombosis. In conditions characterized by a tendency to thrombosis, combined involvement of several coagulation factors is frequently encountered. These complications are denoted by a shift into the direction of increased coagulability of almost all the factors in the coagulogram. Such patterns occur in hepatic disease (fig. 9 ; polygenic thrombosis).

IX—Application of the Coagulogram

The coagulogram patterns described above yield useful information concerning the factors responsible for disorders in coagulation, and thus serve as reliable guides in their treatment.

An analysis of the data in the coagulogram and bedside evidence will help to decide for example whether a given case requires operation, transfusion, or medication (vitamin K, C, P, protamine sulphate, 15, 19 ; antihaemophilic globulin, 18 ; heparin, etc.). The efficiency of the instituted therapy can also be checked by means of the coagulogram.

Investigations with the coagulogram have shown that various coagulation factors may be involved in the pathogenesis of thrombosis. Thus in about 40 per cent. of our thrombotic cases we have found increased values for prothrombin consumption, while in 30 per cent. the disorder could be ascribed to the appearance of labile fibrinogen. In the remaining 30 per cent. thrombosis was due to hypoheparinaemia, hyperprothrombinaemia, etc. In general, each of the haemorrhagic disorders can be shown to have a thrombotic mirror image.

Of course, the repeatedly evidenced tendency to mirror image patterns is valid for therapy, too. While in the presence of haemorrhagic disorders the production of coagulant agents and suppression of anticoagulants should be aimed at (for example by giving antihaemophilic globulin or protamine sulphate), conditions characterized by a tendency to thrombosis call for the suppression of coagulants (with dicumarol, phenylindandion, etc.) and the administration of anticoagulants (heparin, etc.). In such cases the coagulogram helps in the selection of the drugs to be used.

The coagulogram moreover unmasks the presence of compensatory mechanisms by which decreased coagulability owing to a deficiency in certain factors is counterbalanced by an increase in others (20).

Apart from being useful in diagnosis, the coagulogram also renders good services in research work. For instance, in animal experiments it gives information on the consequences of exsanguination and subsequent transfusions (15). It reflects the behaviour of coagulation factors following the administration of plasma or the various plasma substitutes. It closely follows the changes produced by various external factors, such as irradiation, oxygen inhalation, in the elements of blood clotting. The coagulogram is a useful aid in the detection of alterations in clotting factors during the storage of preserved blood, etc.

Experience obtained in the above outlined fields of application confirms the usefulness of the coagulogram.

SUMMARY

Hypo- and hyperfunction of factors involved in the process of blood clotting play equally important roles in disorders of coagulation and may be manifested by an increased tendency to bleeding or thrombosis.

Within these two groups the agents that promote or inhibit coagulation have been classified according to their presence in increased or decreased amounts. By our system based upon their functions it can be shown that the haemorrhagic disorders of coagulation are the mirror images of those due to an increased tendency to thrombosis, and vice versa.

We have pointed out the significance of the complex estimation of coagulation factors in diagnosis and therapy and have outlined the methods for routine tests.

A graphic coagulogram has been constructed for the evaluation of findings. The star-shaped coagulogram

contains the data for twelve coagulation factors. The scales have been set to plot the values for normal blood on the perimeter of the basic circle, while the values for changes in the thrombotic direction are inside, those for haemorrhagic disorders outside the circle. In this way the diagram makes rapid evaluation possible.

The method gives typical coagulograms of each of the various entities under investigation. The type-coagulograms for the common forms of haemorrhagic and thrombotic conditions are discussed and presented. Finally, a review is given of the studies in which the coagulogram has proved to be a useful aid.

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ARREST OF SEVERE PARENCHYMATOUS ORAL HAEMORRHAGES BY THROMBIN INFILTRATION

Prof. Z. FRANKL

Our first report written in cooperation with Litvay on the new method for the use of thrombin was published in 1950. A boy aged 12 suffering from true haemophilia bit his tongue and the resulting severe parenchymatous bleeding could be arrested only by injecting thrombin below the bleeding wound surface (1).

In 1953 an account was given of further cases treated successfully by the above method in dental practice (2). Since then thrombin infiltration has been in use at our Department as a routine procedure and during the past five years since the first trial it has been employed in more than 100 cases.

The term thrombin infiltration instead of thrombin injection is used so as to point out that the technique of introducing thrombin into the system differs from that of the common injection. We refrain from administering thrombin by the intramuscular or subcutaneous route in order to avoid the danger of embolism that may result if the injection is accidentally given into a vein, causing the formation of thrombi.

For this reason thrombin infiltration must be performed with utmost care and it should be repeatedly ascertained by suction whether the tip of the needle has not pierced a blood vessel. When infiltrating, the syringe is to be pushed forward millimetre by millimetre, practically soaking the tissues with thrombin. The tip of the needle should not penetrate deeper than 1 or 2 mm. below the bleeding surface. When the syringe is withdrawn, the puncture canal should also be infiltrated so as to prevent its bleeding. Carried out in this way, the procedure is absolutely safe ; we have not had any complications. In this connection we have to mention recently reported attempts to give thrombin intravenously in cases of severe haemophilia. We disapprove of this practice, because we believe it to be rather risky. With low concentrations the effect is doubtful, while in the case of effective concentrations the possibility of intravasal coagulation and its grave consequences cannot be disregarded.

Thrombin infiltration may be employed as a preventive or as a therapeutic measure. If the patient is known to be haemophilic, any dental or oral surgical intervention is carried out under *thrombin protection*, i. e. the area of operation is infiltrated with thrombin prior to operation. The clot thus produced in the tissue spaces, acting as a biological barrier, will make it possible to perform surgery with very little or no bleeding.

The preparation of the severely haemophilic patient is based on the evidence obtained from the case history, the clinical findings, and the coagulogram (3) ; first general treatment is instituted with the aim of changing the organism. These alterative measures (the administration of Ca, coagulen, vitamin K, vitamin C, transfusions, protamine sulphate, ACTH, etc.) are continued until the coagulogram shows improved values. By the concomitant administration of antibiotics attempts should be made to fight off any acute oral disease, since in the presence of acute infection the tissues are liable to bleed more profusely.

After general preparation, surgical intervention under thrombin protection is, as a rule, uncomplicated. Depending on the severity of bleeding and on the local changes, postoperative wound treatment should include the insertion into the alveolus of a fibrin sponge soaked in thrombin, suturing of the wound margins, biting on a thrombin-soaked covering tampon, etc. The thrombin (thrombofort) and the fibrin sponge (fibrostan) in use at our Department are Hungarian preparations. In part of the cases there is no need to suture the wound, the operation does not differ from a banal extraction and intervention is terminated by simply compressing the alveolar margins. However, in haemophilia or in similar conditions even a continuous pressure bandage may have to be used for arresting haemorrhage.

In such cases, prior to operation a plaster cast is made of the area to be operated on. The teeth to be removed are effaced from the plaster cast and an acrilate plate, similar to a bite-elevator, is made after this model. The tooth or teeth to be removed are then extracted under thrombin protection, a fibrin sponge is placed into the alveolar cavity and on the wound margin, and the acrilate plate is put in place. The opposite teeth bite on the impressions in the masticating surface of the plate and thus keep the area of operation under continuous pressure. To provide for constant pressure, a fixing bandage is put round the head and chin. The plate is left in place for two or three days, then it is removed, washed, and replaced. The fibrin sponge has the great advantage that it need not be exchanged.

Ever since we use high concentrations of thrombin and employ the above surgical technique, it has been rarely necessary to repeat thrombin infiltration.

The thrombin used for infiltration is mostly dissolved in a 4 per cent. pitocaine solution (procaine-adrenalin-posterior pituitary), which is advantageous because the injection of thrombin, a concentrated protein solution, is painful in itself, and anaesthesia is indispensable anyway. Infiltration with thrombin and anaesthesia are thus carried out simultaneously with the same syringe. It must be emphasized that we never use thrombin in conduction anaesthesia. Infiltration is applied exclusively to the area where we wish to elicit a direct haemostatic effect, i. e. where *local* diffusion anaesthesia is usually employed. If, for example in case of lower teeth, conduction anaesthesia is also required, another syringe containing a thrombin-free anaesthetic is used for the purpose.

The usual concentration of thrombin is 1000 U./ml. (The thrombofort powder containing 2000 coagulation units is dissolved in 2 ml. of a 4 per cent. pitocaine solution.) In haemophilia, owing to diminished contraction the clot is reluctant to organize, tends to remain gelatinous, and is therefore more easily expelled. But the bulkier fibrin barrier resists the pressure of blood flow more effectively and is anchored more firmly in the tissue interspaces. The concentration of thrombin may be adjusted to the severity of the case. For the removal of a single tooth 2000 U. are usually sufficient. The highest amount given in one session has been 10,000 U. Injury to tissue or necrosis has not occurred, on the contrary, thrombin infiltration has been found to exert a favourable influence on the course of wound healing.

According to the manufacturers' instructions for the use of thrombofort, it serves the purpose of local tamponade and is unsuitable for injection. Nevertheless, experience has shown that if handled as described above, it can be used without risk also for *infiltration*. The procedure has proved to be superior to any method so far employed for local haemostasis.

Whether the pathological tendency to bleeding was to be ascribed to disturbed blood clotting, to an impairment of thrombocyte production, or to capillary damage, infiltration with thrombin invariably resulted in the formation of a dense, deep-red clot on the bleeding surface, and bleeding was arrested in every case. This uniformity of effect is explained by the assumption that the introduction of thrombin into the tissue interspaces affects the final phase of clotting and the dissolved fibrinogen is converted into fibrous fibrin.

On the basis of this explanation infiltration with thrombin may be expected to fail in producing a satisfactory effect in the presence of fibrinogen pathology. In fact, experience has shown that in cases where pathological bleeding was due to highly increased fibrinolysis, final arrest of bleeding could be brought about only by applying fibrin sponge tamponade and pressure bandage as well.

In the management of bleedings due to tongue biting of patients with haemophilia, good results have been obtained also by infiltration with group-identical fresh blood as recommended by Strehlinger and Kenéz (4). The clot thus produced was so firm that it remained in place, resisting lingual motions.

In the following three typical case histories are presented in brief.

Case 1—M. N., a boy aged 12 years, with true haemophilia, fell and hit the right upper central incisor, the lateral incisor, and eye tooth. The three teeth were loosened, especially the lateral incisor which, by continuous motion, repeatedly injured the gingiva and prevented healing. The intractable bleeding suggested haemophilia and a coagulogram was made. It showed a pattern typical for haemophilia: recalcification time was prolonged and prothrombin utilization was 0% (fig. 1). The tooth had to be removed. The usual methods for haemostasis were supported by thrombin infiltration. The gingival tissues were infiltrated buccally and palatally and, penetrating along the loose tooth into the alveolus, we applied thrombin also intraosseally.

Extraction was absolutely bloodless. After extraction a fibrin sponge soaked in thrombin was inserted into the alveolus and the wound margins were united by silk suture. There was no late bleeding either.

Case 2—V. P., a boy aged 5 years. Diagnosis: Vulnus contusum gingivae et mucosae oris. Haemorrhagia. Bronchopneumonia. Fibrinolysis.

The boy fell and injured his mouth. A contusion, about 2 cm. in diameter, was seen on the alveolar mucosa above teeth 1 and 2. The mucosa was severely injured. Tooth 1 was loosened. Five days after the tooth injury the mucosal wound began to bleed.

A few days later a diffuse, capillary haemorrhage started from the gingival coat of tooth 1. The tooth was extracted under the protection of thrombin infiltration, with pitocaine as solvent (1000 U/ml., total volume 2 ml.); there was no bleeding. However, on the next day, the mucosal wound and the extraction area began to bleed again. Transfusion, vitamin C and K and calcimusc injections were given as general treatment, local thrombin infiltration was repeated (in Dr. Litvay's department) and a pressure bandage applied, but these measures failed to stop bleeding for longer than a few hours. At this point 1 ml. of group-identical blood was injected below the bleeding area. This stopped the bleeding for a few days, but four days later the wound began to bleed again. The patient developed fever (39.2° C). Bronchial respiration typica

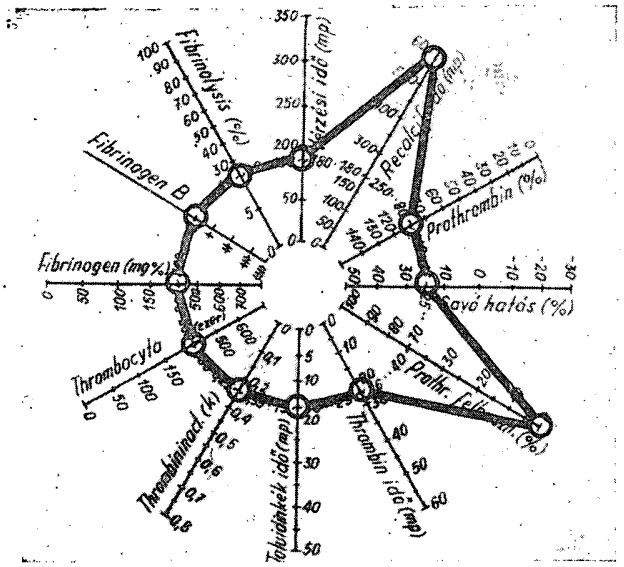

Fig. 1

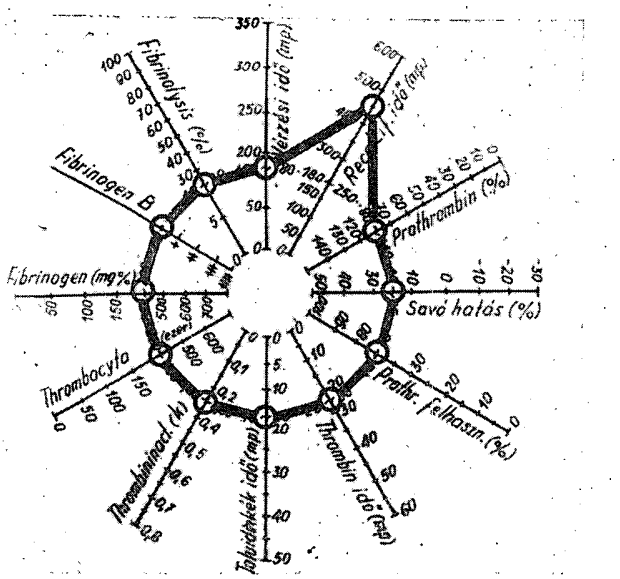

Fig. 3

for bronchopneumonia could be heard over the right diaphragm in an area about 35 mm. in diameter; transfusion was therefore discontinued and streptomycin treatment begun. The patient was remarkably listless and continued to lose blood. The area of haemorrhage was infiltrated again, a pressure tampon of fibrin sponge was placed on the wound margins and held in place by means of an acrilate plate modelled after the plaster cast and head-chin bandage. Bleeding stopped and did not recur The child was afebrile within 24 hours. Transfusion was continued and the patient made an uneventful recovery.

A coagulogram (Gerendás; fig. 2) made two weeks after injury, showed only a prolongation of recalcification time, obviously as a result of transfusions. In another coagulogram made six months later (fig. 3) it was not only the recalcification time that gave an excessive value, there being high peaks for thrombin inactivation and for fibrinolysis too. The high value for fibrinolysis is particularly striking and in our opinion this was the cause of the disorder in clotting.

Case 3—R. B., a boy aged 9 months. Diagnosis: Haemophilia vera.

There were athetoid motions in the left hand as a result of adhesions due to earlier meningeal haemorrhage. A coagulogram (fig. 4) confirmed the diagnosis of haemophilia: recalcification time was prolonged and prothrombin utilization was 0%. Moreover, there was a very marked increase in inactivation and the fibrinogen value was below normal. Twelve hours before admission the patient bit his tongue. A diffuse capillary bleeding oozing from a wound line 2 mm. long was found on the inferior aspect of the tip of the tongue. The mandibular milk incisors were sharp-tipped. The tips were rounded off, 400 U. of thrombin in 0.4 ml. of a 4 per cent. pitocaine solution was infiltrated below the wound margins, resulting in a cessation of bleeding. Fourteen hours later blood began to ooze again, but the oozing ceased

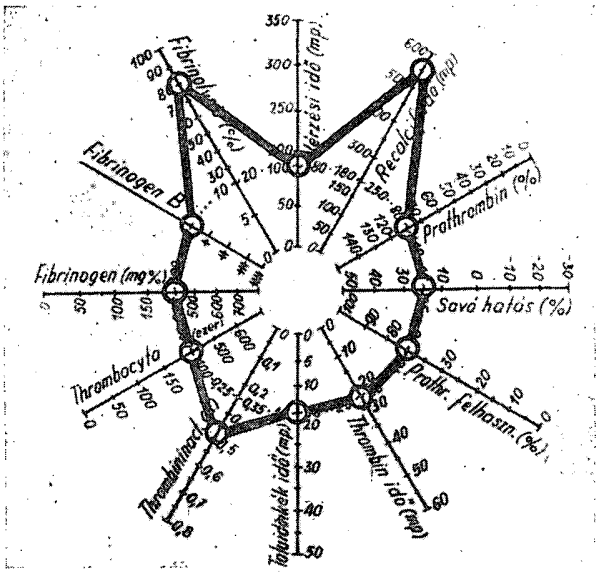

Fig. 2

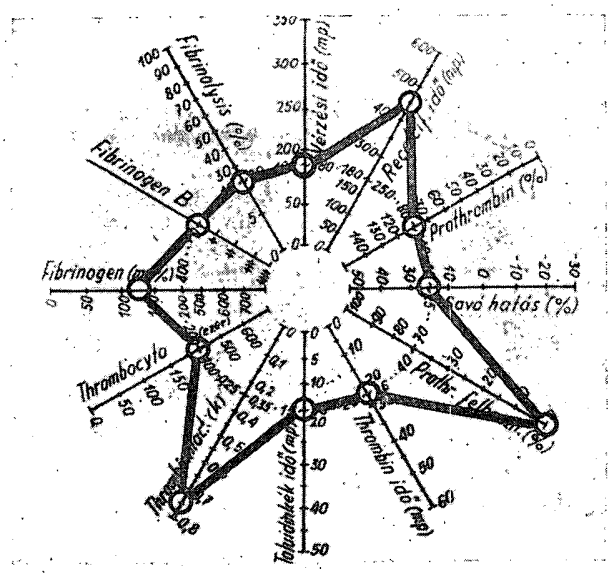

Fig. 4

on daily transfusions (given at Prof. Lukács's department). Five days later the patient began to bleed and this time the haemorrhage could not be arrested by transfusions. 1 ml. of group-identical blood was injected below the wound margins, whereupon the bleeding promptly ceased. The transfusions were continued for a few days in order to replace the loss of blood. Bleeding did not recur and the patient made an uneventful recovery.

SUMMARY

Infiltration with thrombin (thrombofort) has been employed in more than 100 cases during the past five years. Thrombin infiltration with a total volume of 2 ml., at a concentration of 1000 U./ml. has proved to be an absolutely safe and highly effective procedure in the management of severe parenchymatous oral haemorrhage.

In cases where the patient is known to have a tendency to haemorrhage, operations are performed under thrombin protection. General therapeutic measures are never neglected; they are adjusted to actual requirements. For enhancing the local haemostatic action of thrombin the absorbable fibrin sponge is also applied, along with an acrilate plate and pressure bandage if necessary.

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SYMPTOMATOLOGY AND THERAPY OF TONSILLAR DISEASES

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"A sore throat" is one of the commonest complaints encountered by the general practitioner. The pain, the possibility and high incidence of complications associated with acute tonsillar inflammation call for the immediate institution of a deliberate and effective therapy. Considerable information has been accumulated concerning the anatomy, function, diseases, and involvement in other pathological conditions of the tonsils. Possession of this knowledge and of new drugs has rendered treatment of throat affections more efficient.

As to the function of the tonsils nothing definite can be stated as yet. However, experience has shown that removal of the tonsils is not followed by any deficiency symptoms. (The dryness of throat developing or becoming more marked subsequent to tonsillectomy is not considered as a deficiency symptom.) After the wound of tonsillectomy has healed the patient does not become more susceptible to infectious diseases. Recently obtained evidence shows that tonsils which are free from permanent morphological lesions, through their infection and acute disease play a role in the acquisition of immunity. This means that the healthy pharyngeal tonsils of 7 to 9-year-old children and the faucial tonsils up to the end of puberty fulfil immunbiological functions. This recognition throws a different light on the indications of tonsillectomy in the young.

In early childhood the pharyngeal tonsils, in later childhood the faucial tonsils are chiefly involved in acute conditions of the lymphatic pharyngeal ring. The acute inflammation of the lingual tonsil (tonsillitis lingualis) is infrequent and occurs mostly in tonsillectomised individuals.

A detailed description of the symptoms attending tonsillary diseases would exceed the scope of this paper, only a few outstanding features may be discussed. The symptoms of acute pharyngeal tonsillites (adenoiditis acuta) are similar to those of follicular tonsillitis. The posterior wall of the pharynx is almost always inflamed. In children a mucopulurent exudate may hang from the nasopharynx. Rhinitis is part of the picture and also otitis media is a common complication. The latter's course is parallel with that of pharyngeal tonsillitis.

Inflammations of the mesopharynx are also very common. They are collectively termed *angina*. In red angina (pharyngitis acuta) the mucosa coat is affected, while in white angina (tonsillitis follicularis acuta) the tonsils themselves are inflamed. In the former condition the process begins in one section of the pharynx and progresses in an upward or downward direction. Thus hoarseness, tracheitis, in some cases bronchitis may develop, while the ascending form may end with rhinitis. As regards complications and consequences it is a less serious condition than acute follicular tonsillitis. As a rule, follicular tonsillitis begins with chills. At first it is usually unilateral, only to become bilateral later in the course of the disease. Swallowing is extremely painful. The fever is high, but may show individual variations. An uncomplicated case of tonsillitis runs its course within a period of three to five days. The more recent theory on acute tonsillitis assumes infection from the blood stream, as substantiated by the occurrence of shivers prior to the onset of pain in the throat and by the bilateral

character of the disease. The high fever, malaise, and particularly the excessive soreness of the throat during the first days are a serious strain on the patient.

In uncomplicated cases of the above conditions *treatment* may be *symptomatic* or *causal* and should be individualized. Where earlier similar inflammations had been uncomplicated and had taken an uneventful course, and if the actual symptoms promise a favourable outcome (in the absence of intermittent fever, repeated episodes of chills, intolerable pain, peripheral swelling, marked hoarseness, ear complications) decision will favour *symptomatic treatment*, comprising the administration of antipyretics with inherent analgesic effect, as well as local measures. Antipyretics (kalmopyrine, germicide, acetylsalicylic acid, aminopyrine, phenacetin) given at regular intervals help to maintain a constant level of temperature, reducing fever by 1 to 1.5° C and simultaneously alleviating throat pain. Compresses applied on the neck, lukewarm garglings are of beneficial effect. Chamomille tea, bicarbonate of soda, sodium chloride may be used for the garglings. Of course no bactericidal effect can be expected from garglings, but they may help to protect the faucial mucosa, and the mild muscle exercise they induce may contribute to the alleviation of local pain. The use of topically applied drugs should be avoided in cases of acute throat. The rough procedure of painting the mucosa of the throat is dangerous and may precipitate tonsillar sepsis. In mild cases symptomatic treatment usually results in a marked alleviation of symptoms by the fourth day from the onset, with the disappearance of fever and sore throat; after another two days of convalescence the patient fully recovers.

In case earlier throat affections were attended with complications or the actual attack has been stormy in its onset, *causal therapy* is indicated.

Since the responsible pathogenic agent in the majority of acute throat infections belongs to the streptococcus group, it is sensitive to penicillin and sulphonamides. Hence, in the presence of the indications outlined above, *penicillin* is the treatment of choice. In our experience adequate penicillin therapy of acute follicular tonsillitis requires four to five days (the usual time of spontaneous cure in the course of symptomatic therapy) even where general and local symptoms show remarkable regression already on the second day of treatment. It has been frequently observed that the rapid, considerable improvement and bacteriological negativity of the throat resulting from one or two injections of penicillin may be followed by the reappearance of streptococci by the fourth or fifth day; the illness continues in a milder form which may then be cured within a few days by symptomatic treatment. From this evidence it clearly follows that inflammations of the throat or of the tonsils should be treated with penicillin if and when necessary, but once started, penicillin therapy has to be adequate (with daily doses not lower than 300,000 U.) and continued over an adequately prolonged period of time, i. e. four to five days. *Sulphonamides* (ultraseptyl) are also causal agents; their use should also be limited to serious cases. Daily doses of 3 to 5 g., equally distributed, should be administered over a period of at least four days. In cases of acute tonsillitis treated with sulphonamides the period of convalescence may be somewhat prolonged as compared to that seen in the course of penicillin or symptomatic treatment, and complaints of fatigue, malaise, and depression may persist even after the disappearance of local symptoms. As in the case of penicillin, inadequate dosage is frequently followed by a recurrence of tonsillitis or pharyngitis around the fifth day. All these considerations indicate that acute affections of the throat require well-planned chemotherapy, the pros and cons of which must be carefully weighed beforehand.

Data in the literature bear out the fact that in acute tonsillar infections also *bismuth* acts as a factor of causal therapy. In order to be effective it has to be given at the onset of the affection in the form of injection (one daily, a total of two) or, to children, in the form of suppositories (medobis, laryngobis). Although it does not actually shorten the duration of the disease, the administration of bismuth has been found to ensure lower pyrexia and bring considerable relief.

In the light of this experience the combination of penicillin and bismuth appeared to be reasonable. In fact bismocillin, an injection consisting of 1,200,000 U penicillin and of bismuth, has been given extensive trials and produced excellent results. A single dose of 5 ml. maintains an effective concentration of penicillin in the blood for about five days, i. e. the very period during which penicillin therapy is required in acute tonsillitis.

Often the acute throat process is the local manifestation of some infectious disease and may be the most prominent symptom in one of its phases; it is therefore referred to as *symptomatic angina*. In order to set up a correct diagnosis, two examinations are indispensable: *blood count* (quantitative and differential) and the *bacteriological examination of the throat swab*. In the presence of typical throat signs where the history and initial symptoms are also typical, the blood count may be an invaluable aid in unmasking such conditions as e. g. infectious mononucleosis or severe affections of the haemopoetic system.

Vincent's angina (angina ulcero-membranacea, Plaut-Vincent's angina) is usually unilateral, originates from an oral infection and causes more or less serious tonsillar lesions with the involvement of the regional lymph glands. There are only a few general symptoms and the course is prolonged. In these cases local treatment of the tonsils used to be deemed important. With the advent of penicillin a more effective therapy has been made available, bringing recovery within a few days. It is to be pointed out that the therapy of throat affections requires the parenteral use of penicillin. Local penicillin (tablets, etc.) is inadequate in such conditions as it may lead to an unfavourable shift in the equilibrium of the faucial flora and may consequently precipitate serious and unresponsive diseases of the mucosa of the mouth and throat. It is therefore desirable to avoid local penicillin therapy unless necessitated by surgical indications.

Two complications of acute tonsillitis will be discussed in some detail: the locally spreading process of peritonsillar abscess and generalised tonsillar sepsis whose symptoms may supersede those of the local disease.

In typical cases of peritonsillar abscess the healing of acute tonsillitis is followed by a local recurrence of symptoms. The new pain is much more intense than that caused by the initial inflammation, the pain on swallowing is almost intolerable and, owing to the extent of the lesion, referred pain is more marked; at the same time the general condition is much better, systemic symptoms being considerably less developed. The peritonsillar inflammatory process, the most conspicuous symptom, is usually unilateral. In the majority of cases infiltration with pus cells (peritonsillitis phlegmonosa) melts in within a few days and a *peritonsillar abscess* develops. At the very beginning of peritonsillitis intensive penicillin or sulphonamide therapy may help to prevent the formation of an

abscess and, consequently, the necessity of surgical intervention. Although penicillin therapy may suppress the symptoms even in the presence of an actual abscess, recurrences are by no means infrequent and if they occur the picture is usually non-specific, being characterized by the absence of any acute tonsillar inflammation and the rapid development of the clinical symptoms of peritonsillar abscess. This picture of peritonsillar abscess, though formerly rather uncommon, has been increasing in frequency since the advent of penicillin therapy and at the present time it belongs to the typical forms. As regards therapy, sulphonamides, or even more so, penicillin may be effective in the initial stage. In advanced cases, surgery, i. e. incision of the abscess cavity will have to be resorted to.

However, in some cases a simple incision fails to relieve the condition. The tonsil has to be removed by abscessectomy. Removal of the tonsil which represents the anterior wall of the abscess, eliminates the entire cavity. This appears to be the most reasonable and efficacious treatment of peritonsillar abscess. The indications for abscessectomy are :

(1) Failure to ensure proper drainage by incision ; (2) onset of serious bleeding upon incision ; (3) spreading of the inflammatory process over the parapharyngeal area ; (4) the presence of serious general symptoms ; (5) occurrence of glottis oedema.

Abscessectomy is justified in any of these cases.

Tonsillar sepsis is a relatively rare complication of acute tonsillar diseases. In most cases it develops in conjunction with pre-existing acute tonsillitis or shortly after it. Intermittent fever, frequent chills, a prolongation of illness over the above mentioned four- to five-day period are the signs which, among others, may direct attention to sepsis. In numerous cases the patient's condition is aggravated by metastatic purulent inflammations in various organs. The rare, fulminant form of tonsillar sepsis ending fatally within 24 to 48 hours is almost invariably due to anaerobic pathogens. The treatment of tonsillar sepsis must be intensive. If possible, blood cultures and swabs should be examined bacteriologically at the onset of the disease in order to identify the responsible organism. By the aid of tests for sensitivity to antibiotics and sulphonamides the most effective means of treatment is chosen and instituted without delay. Transfusions and vitamins should also be given. Inasmuch as sepsis is not caused by tonsillitis alone but is the consequence of secondary involvement, we should never hesitate to decide on surgery, in addition to medical treatment. Abscessectomy, surgery of the areas adjacent to the involved large vessels of the neck, external drainage of the parapharyngeal regions may be necessary measures ; all this will serve in many cases as an introduction to tonsillectomy, which, when indicated, will have to be performed even in the presence of acute tonsillitis, and is feasible in one sitting.

Chronic inflammation of the faucial tonsils (tonsillitis chronica) presents little if any difficulty in therapy, but it does involve diagnostic problems. There is furthermore the question to be dealt with whether in the actual case the so-called focal disease is in any connection with the chronic inflammation of the tonsils.

Chronic tonsillitis lacks any clear-cut pathological and clinical definition. During life the tonsils, more or less independently of previous acute inflammations, are being subjected to continuous lesions and over 20 years of age the more or less marked signs of chronic tonsillitis may be detected in almost every individual. It is therefore justified to speak of a state of chronic tonsillitis and it should be decided in each case whether at the moment of examination the chronic tonsillitis is to be considered active, whether it may be held responsible for the patient's complaints, i. e. whether it represents a focus precipitating or maintaining some other, actually present pathological condition. In chronic tonsillitis the histological signs of inflammation and healing may be found side by side both in the substance of the tonsil and in the peritonsillar tissues. Scars may be detected deep within the tonsils and peritonsillarly, with pockets of poor blood supply among them, the importance of which from the point of view of focal infection is well known.

The *case history* is an important factor in setting up the diagnosis of chronic tonsillitis. Uncertain complaints of a sore throat, repeated episodes of acute tonsillitis, preceding peritonsillar abscess are valuable points in the case history. As to focus diagnosis, another disease developing on top of a pre-existent acute tonsillar affection may confirm suspicion of a tonsillar focus. Of *local signs* redness and hyperaemia of the soft palate, faucial pillars, and anterior pillars are of significance. On the other hand, the size of the tonsils and the appearance of the tonsillar surfaces are inconclusive, except for unilateral swelling of a tonsil. Palpability, tenderness of regional *lymph glands* may direct attention to the activity of the condition, even in the absence of acute signs. At present, one of the most important diagnostic aids is the *expression of the tonsils*. This method provides information not only of the presence of the tonsillar and peritonsillar scars but also of the properties of any exprimate obtained. A dense detritus originating from the upper pole of the tonsil has practically no diagnostic significance. If the exprimate is *purulent*, whether thin or dense, it will be particularly valuable as a diagnostic aid provided it reappears on examinations carried out at intervals of a few days. The purpose of tonsillar expression is therefore twofold : (1) The finding of fixed tonsils reveals the presence of scars and pockets, which, as has been mentioned, are the structural prerequisites of the development of focal infection, and (2) examination of the exprimate may yield data showing the actual participation of inflammatory processes in chronic tonsillitis.

On the basis of the foregoing, the only justified *therapy of chronic tonsillitis* appears to be the *radical removal of the tonsils*. This method ensures the elimination of areas lacking adequate blood supply between the scars in the tonsils as well as the liberation of adhesions. All conservative measures yield doubtful, if any, results. The contraindications of tonsillectomy are rapidly dwindling.

As to the *time of operation*, as a rule no surgery is undertaken within six weeks after acute tonsillitis. Peritonsillar abscess may be operated even in the presence of an acute inflammation, but, if conditions permit, tonsillectomy is postponed by six weeks. In the presence of secondary disease it is preferable to wait until its acutest phase is over, but this delay must not exceed reasonable limits. If the secondary disease takes a prolonged course, the process of healing may be accelerated by tonsillectomy. Focal diseases are not regarded today as bacterial metastases ; however, tonsillectomy being so frequently followed by bacteriaemia, in the presence of an active secondary disease (carditis, nephritis), daily 400,000 U. penicillin

should be given for three days around the day of operation. Some measure of safety may be afforded by the administration of 2 g. aminopyrine daily. For such protection large doses of salicylates are not favoured owing to reports in the literature confirming their haemorrhagic action. The less imperative the need of operation the more carefully should the contraindications be weighed, paying particular attention to diseases of the haemopoetic system, active tuberculosis, and of local symptoms to dryness of the pharynx which is liable to deteriorate after tonsillectomy.

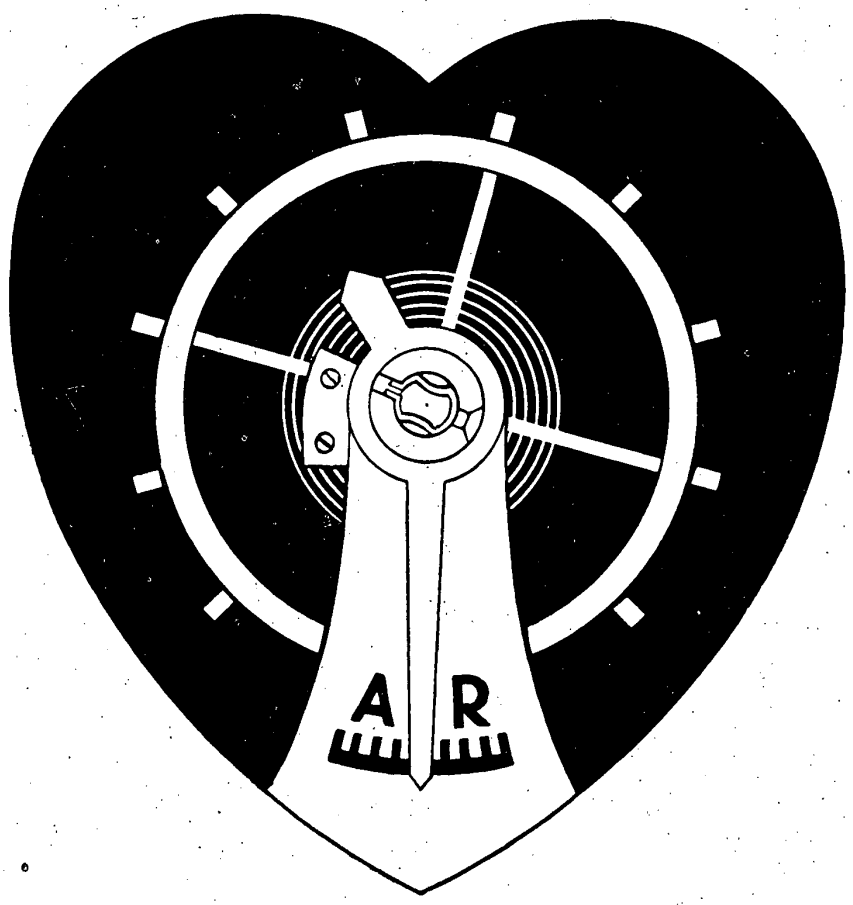
As regards *age*, tonsillectomy is usually too great a strain on children under 4 years of age. In advanced childhood age is of little significance, it is the condition of the whole organism and, in particular, that of the circulation which counts. Adenotomy may be performed at any age, even under 4 years. Adenotomy by itself may favourably influence tonsillar inflammations in young children.

As regards the *technique of surgery*, it should be mentioned that children are operated under short general anaesthesia and Sluder's instrument is used for the total extirpation of tonsils; in adults local anaesthesia is the method of choice. Penicillin added to procaine has been found to offer no advantages in the operation of chronic tonsillitis, while it is indicated in surgery for acute cases of tonsillitis. Prior to the operation novatropine or atropine should be injected to reduce salivation, whereby surface anaesthetics, pantocaine or cocaine, may be applied with much greater economy. After atropine 0.5 per cent. pantocaine-epinephrine may be used instead of the 2 per cent. solution.

Malignant tumours of the tonsils and mesopharynx deserve special notice since they may lead to diagnostic errors in connection with acute tonsillar diseases. For instance tonsillar malignancy may be mistaken for Vincent's angina or may simulate peritonsillar abscess. It has already been emphasized that in atypical cases of tonsillar and faucial conditions we cannot be lavish enough with bacteriological and haematological examinations. In typical cases, particularly in old age, the possibility of *malignant growth* should always be borne in mind. If the tonsillar affection is

(1) unilateral,
(2) takes a prolonged course,
(3) if it causes few and uncertain complaints,
(4) if the tonsils are too firmly adherent to adjacent tissues,
(5) are of firm consistency,
(6) bleed profusely on attempts at expressing their contents, and
(7) particularly when the regional lymph glands are hardened,

malignancy should always be suspected. Differential diagnosis is particularly difficult in cases of sarcoma, as this malignant growth may occur in young individuals, may be bilateral and may be associated with enlargement of the lymph glands of the neck. *The very slightest suspicion of malignancy calls for histological examination*, irrespective of the unilateral or bilateral epithelial or connective tissue nature of the suspected malignant growth. *The diagnosis must be clarified but not by tonsillectomy*. Experience has shown that in cases of malignant growth of such localization the outcome of the operation is most unfavourable; to arrive at the correct diagnosis at the earliest possible time is therefore all important in order to avoid operation in these cases. The modern therapy of such conditions is treatment by irradiation. In the presence of malignant growths surgery should be restricted to electrocoagulative treatment of the post-irradiation tumour-remainder or—in case the primary growth has shown adequate response to radiotherapy—to radical removal by block dissection of the usually radio-resistant lymph gland metastases.



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CONTRIBUTIONS TO DIENCEPHALIC AUTONOMIC EPILEPSY, WITH SPECIAL REFERENCE TO A CASE CURED WITH CHLORPROMAZINE

Prof. G. NYIRŐ, Dr. A. SZOBOR, and Dr. I. SOÓS

In a report published in 1929, W. Penfield described a peculiar type of seizures under the heading "Diencephalic Autonomic Epilepsy". The complicated paroxysms presenting almost exclusively with autonomic manifestations occurred in a female aged 41 years who had a tumour compressing bilaterally the foramen of Monro.

In his first, classical case Penfield distinguished the following phases in the seizure pattern: 1. The prodromal phase (restlessness). 2. A sudden vasodilatation in the area of the cervical sympathetic system, accompanied by a synchronous rise of blood pressure. 3. Lacrimation, sweating, salivation, bulbar protrusion, pupillar dilatation or contraction, increase in the rate and amplitude of the pulse, pilomotor symptoms, slowing of respiratory rate, and sometimes loss of consciousness. 4. Disappearance of dermal flush, fall of blood pressure, slowing of pulse rate and weakening of the pulse. 5. Hiccuping. 6. Transient chills. 7. Cheyne-Stokes' respiration (a result, and not an accompanying feature, of the seizure).

Penfield ascribes the seizure to a discharge in the area of the unilateral or bilateral dorsal thalamic nucleus; he assumes that the discharge spreads along the gray matter of the third ventricle (paraventricular, supraoptic, tuberal, mamilloinfundibular nuclei, corpus mamillare, subthalamus).

According to Penfield the gray matter adjacent to the third ventricle includes the representation of various visceromotor functions, such as vasomotor activity, respiration, thermal regulation, pupillary control, glandular secretion (perspiration, lacrimation, salivation). He draws a parallel between the purely diencephalic autonomic seizure elicited exclusively by diencephalic discharge, and the motor Jacksonian seizure of solely cortical localization. Penfield emphasizes that the main representation of the autonomic system lies in the diencephalon, the medulla oblongata containing subordinate centres and the cortex control centres. Subsequent observations and animal experiments have revealed that the anatomical basis of the Penfield seizures is to be sought in hypothalamic, rather than thalamic, discharges; Penfield himself revised his view later.

Three further cases of diencephalic epilepsy have been described by Penfield; none of them represents the full-blown pattern of the seizures.

Apart from these four cases, Penfield has in one instance found facial and cervical flush occurring upon stimulation of the infundibulum, and in another case removal of a tumour of Monro's foramen provoked a seizure consisting of urticaria and itching.

The second classical case of the disease was described in 1945 by Engel and Aring. The patient, a male aged 17 years, had a cystic degeneration in the dorsomedial and lateral nuclear area of the right thalamus. The attack began with an aura, coryza, shivering, chills being the presenting symptoms. The skin was pale and cool although the rectal temperature rose rapidly. Further characteristic symptoms were tachycardia, fluctuating blood pressure, gastrointestinal hyperactivity (vomiting, nausea, diarrhoea). The end of the seizure was marked by a critical fall in temperature accompanied by excessive sweating and erythema. Sometimes a seizure would last as long as two days and was characterized by extreme fluctuation in blood pressure. A seizure of longer duration resulted in a weight-loss up to 2 or 3 kg. The attack was elicited by intercurrent disease or emotional stress and was associated with extreme anxiety. Engel and Aring believe the seizures to be hypothalamic in origin, the hypothalamic release being due to a disruption of corticothalamic inhibition by a thalamic focus.

Apart from the cases of Penfield and of Engel and Aring, diencephalic seizures have been described by Ischtschenko, Lhermitte, Thiébaut et al., and Urechia, but these were abortive cases, vegetative crises or affective explosions, which cannot be ranged into the pattern of diencephalic autonomic epilepsy.

The diencephalic origin of the phenomena encountered in the autonomic epilepsy of Penfield has been corroborated by numerous observations, physiological, clinical, and surgical, as well as by ample experimental evidence.

On stimulating the dorsal lateral portion of the hypothalamus in the cat by means of a Horsley-Clarke apparatus, Ranson elicited a response including dilation of the pupils, slow breathing, salivation, piloerection, fits of rage, and inhibition of gastrointestinal activity. The "hypothalamic animals" of Bard showed a similar response to mild stimulation. These seizures are thought by Bard to be the equivalent of anxiety reaction in the normal animal. Hess and Akert (1955) have confirmed this view, rejecting the terms "pseudoaffect" and "sham rage" as superfluous. Bard's experimental animals showed a significant rise of adrenalin and sympathin in the blood.

According to Grinker, it stands beyond doubt that the central representation of the emotional expression of rage and anxiety (and of the accompanying vegetative symptoms as well) lies in the hypothalamus. Morgan has reported on convulsions in dogs with foci in the level of the third ventricle; the presenting symptoms were salivation, dilation of the pupil, general vasoconstriction, tachycardia, hypertension, and relaxation of the anal and urinary sphincter.

Dealing with autonomic seizures, Fulton emphasizes that discharges in both the sympathetic and parasympathetic system are involved in the seizure and that, in general, the stimuli from the two systems "overlap". According to Grinker the sympathetic and parasympathetic responses, fragmented and mixed, appear with alternating predominance.

Increased salivation and lacrimation have often been recorded by Foerster and Gagel as occurring in operations on the hypothalamic region; they observed a general hyperhydrosis in one case and an attack of vasodilatation in an other.

Of exceptional importance are the electric stimulation experiments of Hess who, by stimulating the posterior hypothalamic area (supramamillar region, mesodiencephalic transition, proximity of the orifice of the aquaeduct, tectum, pretectum) elicited mydriasis, elevation of blood pressure, acceleration of pulse and of respiratory rate, as well as motor excitation *(dynamogenic-ergotropic zone)*. Stimulation of the anterior hypothalamus (the suprachiasmatic area, the

zone of the anterior commissura, the anteromedial part of the thalamus, the preoptic area) caused a narrowing of the pupil, a fall in blood pressure, bradycardia, salivation, passage of urine, general relaxation and adynamy *(endophylactic-trophotropic zone)*. Hess could elicit also an effective defense reaction in the cat by stimulation of the perifornical area, the preoptic, ventral, septal areas, and the central mesencephalon.

The parasympathetic nature of Hess's trophotropic zone has been confirmed by Cushing's experiment: during operation, pituitrin or pilocarpine was injected into the lateral ventricle of the brain and, if Monro's foramen was patent, parasympathetic excitation could be elicited. The patient began to sweat profusely all over the body, with reddening of skin. Systolic blood pressure fell, gastric and intestinal peristalsis increased, rectal temperature and basal metabolism diminished. The hypothalamic origin of these parasympathetic excitation symptoms is confirmed by Cushing's observation according to which pituitrin injected into the lateral ventricle is absolutely ineffective if the foramen of Monro is occluded or the hypothalamus is destroyed by malignant growth. Henderson and Wilson injected acetylcholine intraventricularly and thus elicited parasympathetic attacks which could be relieved by intraventricular administration of atropine. Intraventricular epinephrine was ineffective.

From Hess's experiments and subsequent observations by de Morsier the diencephalon is known to have also motor and sensory functions; stimulation of the hypothalamus may therefore elicit motor excitation. The presence of a sensory disturbance of diencephalic origin suggests a disorder in the dynamization of the sensoroperceptive system. The diencephalon is looked upon as a "collective representation" of the whole organism (Peters).

The evidence outlined above makes it obvious that the diencephalic autonomic epilepsy of Penfield is based on a fragmentedly alternating excitation of the ergotropic and trophotropic zones of the hypothalamus (Grinker, Bucy, de Morsier) by a chain of overlapping sympathetic and parasympathetic stimuli.

Below we present the description of a case of typical, complete Penfield seizures observed by ourselves. Penfield described the first classical case in 1929, later Engel and Aring reported on the second; hence our case represents the third instance of typical, complete autonomic epilepsy of purely diencephalic nature published in the literature.

A female aged 20 years was admitted December 16, 1954, for peculiar seizures of which she had been suffering for several years. *Anamnesis:* Familial history was noncontributory. Menstruation was normal, there had been no childbirth or abortion. She did not smoke or consume alcohol, nor was she addicted to any narcotic. At the age of 16 (in 1950) tonsillectomy had been performed. As told by herself, she had sustained an electric trauma to the skull, had fallen and lost consciousness for a short time. As to the intensity, quality, and duration of the electric current that hit her, no reliable evidence could be obtained.

The first seizure developed a few days after the electric injury. Without any warning she suddenly felt ill, dizziness accompanied by an unpleasant tenseness in the head compelled her to sit down. Shortly afterwards she experienced violent temporal pulsation, profuse sweating and lacrimation. In about 10 to 15 minutes the seizure ended with chills; it was followed by dizziness and exhaustion, leaving an impression of dread in the patient. During seizure she did not lose consciousness or pass urine, nor did she bite her tongue or have any extremital convulsions.

The first attack was soon followed by several others of similar character and increasing frequency. During seizure blood pressure rose to very high levels (more than once to 280 mm Hg systolic and 170 mm Hg diastolic), accompanied by a high pulse rate of 160 to 180 beats per min. There had been two longer seizure-free periods, apparently unrelated to changes in her circumstances. Later the seizures came on every day and about one year before admission she began to have several fits a day (1 to 9). Though variable in depth, intensity, and duration (from 1 or 2 minutes to 1 ½ hours), the seizures were closely similar to the first. In time she came to recognize the prodromal change in general well-being, the intrathoracic distress, anxiety, and intracranial tension as the introductory signs of an attack. Moreover—up to a certain degree—she could judge in advance the severity of the impending seizure from the nature and intensity of the introductory changes. In seizure-free hours she felt quite healthy; however, when several fits followed one another she spent the day mostly in bed, feeling totally exhausted, without ever losing consciousness.

Seeking relief from her affliction, she was treated at several clinics and hospitals; her symptoms were usually ascribed to hysteria or vegetative crisis. Also phaeochromocytoma has been suspected. She had been given a wide variety of drugs (central vasodilators, intravenous bromine salts, barbiturates) to relieve or to prevent seizures. It is noteworthy that one of the numerous attempted therapeutic procedures, the injection of allyl-cyclohexenyl-thiobarbiturate sodium, alleviated the seizure but gave rise to excessive excitation, psychomotor agitation, anxiety, and as soon as the narcotic effect was over the attack continued at full intensity.

Repeated and prolonged hospitalization, the massing of seizures, and the deterioration in her condition gradually deprived the intelligent patient of any hope of recovery, she even came to regard her illness with a kind of indifference.

On *admission* she was found to be moderately developed and undernourished. Physical examination, chest X-ray revealed no pathology. The ECG was normal. In the seizure-free period blood pressure was 100 to 120 systolic, 80 mm Hg diastolic. Pulse rate was slow (46 to 52/min.). No appreciable organic neurologic pathologic symptoms could be detected. The lateral X-ray plate of the skull showed no abnormality, the sella was intact. Eye examination showed the visus to be 5/5; ocular vessels were normal and the fusion frequency FF: $\frac{20-22}{20-22}$. Visual fields (white, coloured) were complete, the blind spot was normal. During seizure the vessels in the fundus were moderately narrowed. The oto-rhino-laryngological examination revealed no nasal, pharyngeal, or sinus pathology. Hearing was unimpaired, vestibular reaction was normal. EEG and pneumoencephalography during a seizure-free period disclosed no pathologic changes. To exclude the possibility of phaeochromocytoma, renal radiography, intravenous pyelography, and bilateral perirenal insufflation were done, but no changes were found. Histamine failed to challenge a seizure.

Of the numerous laboratory tests the following are pointed out: Urinalysis was normal. Wassermann test, negative both in blood and CSF. ESR (Westergren): 5 mm. in 1 hour, 8 mm. in 2 hours. Quantitative and differential blood counts: normal, with no significant change occurring during seizure. CSF by lumbar puncture: normal. Ca, P, and K in blood were normal. The tests for blood sugar (including tolerance tests) yielded normal values both in the seizure-free periods and during seizure. Water metabolism was normal. An intravenous atropine test (0.01 mg.) caused tachycardia but no substantial rise in blood pressure (flat curve type).

Mental condition: Depressed basal mood, marked dysphoria; the patient showed indifference concerning her disease and did not believe in recovery. Psychotic symptoms were absent. As to social behaviour, she was moderately uncritical, especially regarding the sexual sphere. Though a virgin, her behaviour and sphere of interest suggested a definitely hypersexual

attitude, verging on the pathological. The Ranschburg test for memory showed an immediate loss of 24 per cent. and at 48 hours a 36 per cent. loss as compared to the normal values of 14 and 16 per cent. respectively. The impairment of memory may be considered a mild psychoorganic symptom. Her intellect was intact.

During the 91 days of treatment at our Clinic she had several seizures daily; the paroxysms were essentially of the same pattern, though there were wide variations in intensity. She had mild attacks lasting a few minutes, as well as intractable, grave seizures of several hours' duration, recurring many times a day. Analysis of a moderate or grave seizure disclosed the following phases:

(1) *Prodrome (aura).* Usually a prodrome of a few minutes' duration or an aura of a few seconds in length occurred; the feeling of general well-being changed, anxiety, uncertainty, oppression, pulsation and tightness in the temporal area developed. The knowledge that these symptoms would inevitably bring on a seizure filled the patient with terror. In this phase blood pressure and pulse rate were unaltered and the patient looked pale and anxious. By the end of the prodromal phase she became very weak, which compelled her to sit or lie down.

(2) Actual onset of the seizure was marked by a sudden *dilatation of blood vessels*, extending over the face, skull, neck, and the cervical part of the chest (to the part supplied by the cervical sympathetic). Meanwhile, temporal pulsation developed into a violent, diffuse headache of vasodistensive nature. Blood pressure rose rapidly, to higher than 260 to 280 mm Hg systolic and 200 to 240 mm Hg diastolic, hence amplitude was relatively very narrow. At the same time the pulse became thready and fast (140 to 180/min.). Blood pressure and pulse rate varied within extremely wide limits throughout the seizure and even within one minute. These excessive oscillations in blood pressure were followed by smaller changes in the pulse (fig. 1).

(3) On a few occasions, a dextroadversive torsion of the head was seen and sometimes even the hands showed athetoid torsive movements. This motor feature usually overlaps into the next phase of the seizure, depending in duration on the severity and duration of the attack.

(4) In this phase intense lacrimation, then tear-flow developed, with conjunctival injection and chemosis, subsiding slowly, in about 20 to 30 minutes after cessation of the seizure. The pupils were usually dilated and the bulbs protruded. Intense sweating, salivation, and very marked piloerection were observable. Usually in this phase strong gastrointestinal activity also developed, accompanied by rumbling and eructation. Blood pressure continued to rise, the pulse amplitude was extremely narrowed and pulse rate reached the maximum. This phase may be looked upon as the climax of the seizure, the gravest stage which is extremely distressing for the patient. The seizure then came to an end, partly by crisis, partly by lysis.

(5) Blood pressure suddenly fell to normal levels, the pulse rate slowed down to bradycardia, with the pulse full, well palpable; facial flush, salivation, sweating, tear-flow disappeared in a few minutes, piloerection, conjunctival injection, chemosis began to subside, the pupils became narrower and the bulbs began to retract.

(6) The cessation of sweating was followed by a few minutes of remarkably violent chills, though the patient remained afebrile.

(7) When the whole attack was over the patient was very pale, tired, exhausted, and usually fell asleep for half to two hours. After grave or recurrent seizures she complained of dull headache and dizziness.

(8) Continual or grave seizures brought about a significant loss in body weight, leading gradually to emaciation.

While at our Clinic, the patient had several attacks of the above nature. A detailed analysis of the seizure pattern will show the following differences as compared to the first, classical case described by Penfield:

(a) In our case excessive exhaustion appeared in the prodromal phase; Penfield has not observed this. (b) Penfield makes no mention of the high lability and fluctuation of blood pressure and pulse, which did occur in the case of Engel and Aring as well as in ours. (c) Penfield's patient showed no motor phenomena; in our case adversive rotation of the head and athetoid movements of the hands were often seen during the attack. These we believe to be *sui generis* motor excitation symptoms of diencephalic origin (Hess, de Morsier). (d) Our patient developed considerable chemosis in phase 4 of the seizure. (e) Respiratory rate did not change appreciably during the seizure and after it there was no Cheyne-Stokes' respiration which in his own case Penfield regarded as a sequel to the seizure. (f) There was no hiccuping in the last phase of the seizure, while in phase 4 there were pronounced gastrointestinal phenomena (intestinal rumbling, eructation). According to Penfield, the diencephalic representation of the alimentary tract is small, but compared to other autonomic funtions it has a relatively large cortical representation (in the insular cortex). Penfield believes that this accounts for the rare occurrence of alimentary tract automatism in diencephalic autonomic epilepsy. (g) Finally, our patient did not lose consciousness, apparently because the stimulus did not spread to areas important from this point of view.

Several attempts have been made at our Clinic to alleviate or block the seizures. Vasodilators, barbiturates, bromine salts, hydantoin derivatives,

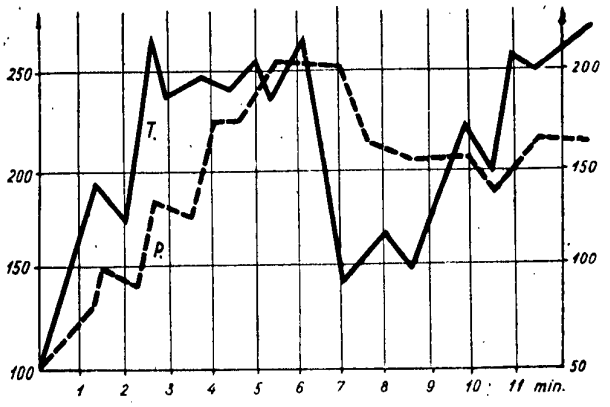

Fig. 1

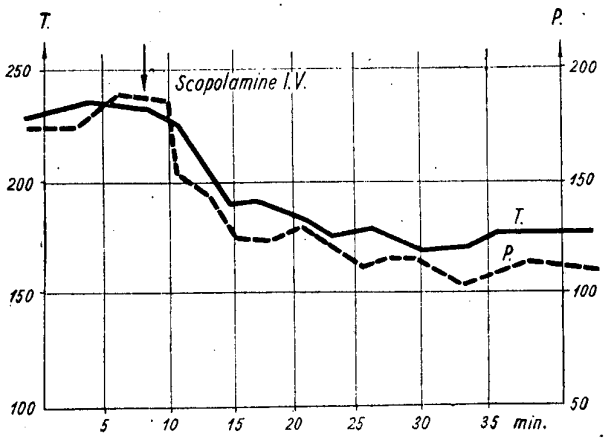

Fig. 2

valeriana preparations, all failed to bring about the desired effect.

We have noted the transient effect of allyl-cyclohexenyl thiobarbiturate sodium in an intravenous dose of 0.60 g., but the excitation was stormy and once the patient was awake the seizure continued. We have produced noteworthy effects (repeatedly) by giving 0.1 to 0.3 mg. of scopolamine hydrobromide intravenously (fig. 2). Very slow injection was followed in 1/2 to 1 minute by a slight reduction in blood pressure and pulse rate, and by arrest or significant relief of perspiration, salivation, and tear-flow, i. e. by scopolamine the parasympathetic component in the seizure could be blocked. There was, however, no change in the duration of the fit.

In an effort to alleviate the sympathetic symptoms the stellate ganglion was blocked with procaine hydrochloride. This was followed in about 2 to 3 minutes by a marked reduction in systolic, and a less marked diminution of diastolic, blood pressure, and a moderate decrease in pulse rate ; yet, in 8 to 12 minutes the seizure continued with its original intensity (fig. 3). Sweating, facial flush, salivation, and lacrimation remained unaffected. Intravenous TEAB produced a transient fall in blood pressure and intravenous atropine (0.02 mg.) temporarily alleviated the parasympathetic symptoms.

The undoubtedly diencephalic nature of the seizures and the alleged diencephalic mode of action of chlorpromazine induced us to give the drug a trial.

The attempt has met with success : The intravenous injection of 12.5 mg. of chlorpromazine (4560 R. P., largactil, chemically chloro-3 [dimethylamino-3' propyl]-10 phenothiazine hydrochloride), diluted in saline was followed by arrest of the seizure within four minutes (fig. 4). This effect could be reproduced in any subsequent attack, and even paroxysms of excessive severity could be stopped within three to ten minutes. In view of the excellent effect of chlorpromazine, the patient was started on largactil tablets, with twelve times 1/2 (12.5 mg.) as initial dose. This was gradually reduced later. In the first week already the seizures became less frequent and occurred as abortive attacks of diminished intensity which could be relieved by intravenous chlorpromazine. When discharged (March 17, 1955) the patient was taking four times 1/2 tablets of chlorpromazine daily, which dose was reduced to three times 1/2. At present she is practically free from seizures, except for slight discomfort of one to two minutes' duration occurring at three to four week intervals and ceasing spontaneously. If for some reason she fails to take the drug the spells develop more frequently but are by far less intensive and of shorter duration than had been the earlier seizures. When last seen (September 10, 1955) her condition was good, she was free from seizures on daily three times 1/2 tablets of chlorpromazine ; she has put on weight and returned to work feeling perfectly fit, physically as well as mentally.

Discussion

The case under review is undoubtedly one of autonomic epilepsy of diencephalic origin in whose pathogenesis an electric trauma to the skull is looked upon as having been of causal significance. The patient's history and the findings at examination practically exclude any other etiological factors (such as tumour, encephalitis). Although no reports have been published so far on the development of diencephalic epilepsy or similar paroxysms following electrotrauma to the skull, in our case the chronological and causal relationship between the electric trauma to the skull and the development of diencephalic seizures is obvious. In numerous pathological and clinical observations concerned with electric injury to the central nervous system mention is made of morphological changes in the gray matter adjacent to the third ventricle, and of the subsequent permanent, central and vegetative symptoms. For example according to Jenny, Jellinek, Schridde it is mainly in the environment of the third ventricle, Sylvian aqueduct, and fourth ventricle that haemorrhages (per diapedesin, and less frequently per rhexin; Kawamura, Pollack) are liable to occur. In animal experiments, Zolotov and Zynkin have found grave lesions of the vegetative ganglia (vacuolisation, swelling, chromatolysis, nuclear lesions).

The above outlined morphological changes offer no help in the evolution of a uniform pathogenetical view. The following may be listed as noxious factors :

1. Penetrating heat injury (Jenny, Jellinek, Panse, Schridde) and colliquation necrosis (Peters). 2. Vasoparalysis, stasis (bleeding per diapedesin) or per rhexin, consecutive emollitions ; Koeppen, Lange, Jenny). 3. Impairment of colloidchemical structure, temporary (Peters) or permanent (Linck), permitting analogy to the commotional upset of colloidchemical balance as described by Hallervorden.

On the basis of the aforementioned morphological alterations the clinical signs of vegetative-regulative disturbances, reminiscent of the postcommotional syndrome (Peters), develop subsequently. According to Lange, electrotrauma affects the entire vegetative system. Reichardt speaks of a "central-vegetative vital reaction".

In our case the electric injury to the hypothalamus was manifested in diencephalic autonomic epilepsy

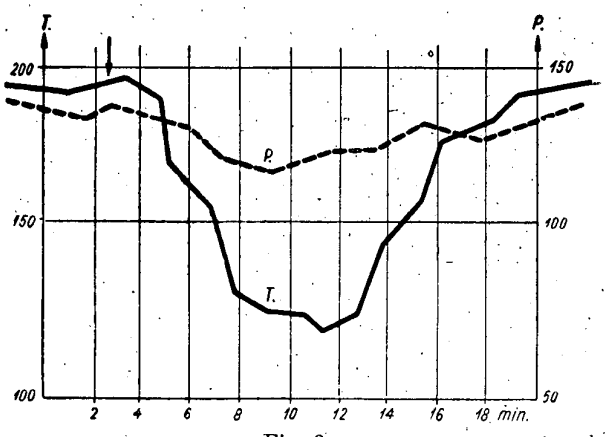

Fig. 3

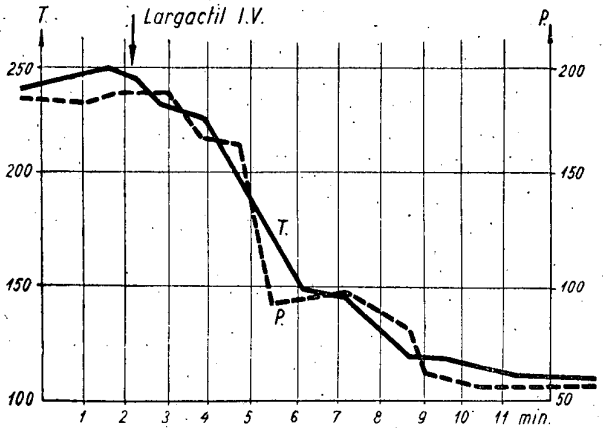

Fig. 4

and a moderate sexual aberration in personality, the latter being attributed to a chronic irritation of the tuberal nucleus.

Since central sympathicolytic, parasympathicolytic, as well as antiepileptic agents failed to bring relief, we decided to try largactil and have thus been the first to make an attempt at blocking diencephalic autonomic seizures by the administration of chlorpromazine. Most workers claim that chlorpromazine has its site of action in the diencephalon, although Delay et al. believe it to be an agent reducing tissue metabolism. It has been shown in animal experiments (D. Anton-Stephens) that chlorpromazine blocks the hypertensive effect of adrenalin and nor-adrenalin, inhibits autonomic functions of sympathetic nature, but at the same time exerts a moderate anti-acetylcholine activity. It is also a mild antihistamine agent. In their animal experiments Reilly and Tournier have proved that the above actions of chlorpromazine take place in the level of the diencephalic vegetative centres.

Observations made in cases of various forms of psychoses support the diencephalic localization of the action of chlorpromazine. According to Staehelin, the drug is most effective in emotional psychoses and in the brain stem syndrome; he goes so far as to call it a medicament having affinity with the brain-stem ("stammhirnaffines Medikament"). Kielholz points out the excellent effect of chlorpromazine on vegetative dystonia associated with exogenous or endogenous depression and emphasizes that it is more efficient in agitated, than in inhibited, depression. It promptly blocks the withdrawal symptoms in narcomania.

Labhardt has found chlorpromazine to be equally effective in the hyperphrenic-hyperkinetic phase of diencephalosis, in eretic idiocy, and in hysteroid reactions. Janzarik has claimed the drug to be effective in psychoses that can be traced to diencephalic localizations. The side-effects of prolonged chlorpromazine treatment (hypotension, adynamia, reduction of saliva and tear excretion, marked inhibition of the affective components of personality, diminution of psychomotor activity, sometimes to a parkinsonoid level) all tend to confirm the view that the drug has its site of action in the central-vegetative area (Staehelin, Lehmann, Anton-Stephens, Avenarius).

In interpreting the mode of action and site of action of chlorpromazine, Lehmann has relied upon the experiments performed by Magoun et al. According to the latter authors, the reticular system of the mesodiencephalon represents an activating or dynamising centre whose role comprises the maintenance of wakefulness and attention, as well as the mediation of affect responses to external stimuli. In animals, simultaneous injury to the caudal hypothalamus and oral mesencephalon produces a syndrome comparable in pattern to chlorpromazine effect. According to Lehmann, chlorpromazine blocks both the sympathetic and parasympathetic portions of the reticular system, hence it is justified to speak of "chemical mesencephalotomy" which inhibits the "visceropsychic activity" of the central nervous system in the first place.

The curative effect of chlorpromazine on the diencephalic autonomic epileptic seizures in our case is believed to be further, though modest, evidence showing that the site of action is in the hypothalamus. However, this action is not confined to the dynamogenic-ergotropic zones, it has also an endophylactic-trophotropic site. In view of the therapeutic success experienced in this case, we believe chlorpromazine (largactil) to be suitable for use in the treatment of post-traumatic diencephaloses and in disturbances of central vegetative regulation.

SUMMARY

(1) The described case of complete diencephalic autonomic epilepsy (Penfield) is the first in Hungary and the third in world literature.

(2) The evidence derived from our case corroborates the view—substantiated by experimental investigations and data in the literature—that autonomic epilepsy is diencephalic in origin.

(3) The seizure pattern seen in our patient is analysed in the light of the classical description given by Penfield and it is stated that the sympathetic and parasympathetic stimuli were overlapping but fragmented.

(4) Chlorpromazine has been administered for the first time in diencephalic autonomic epilepsy.

(5) A survey of the literature on the pathoanatomy, genetics, and clinic of electric injury to the skull is presented and the causative role of electric injury is pointed out in our case.

(6) The cure effected by chlorpromazine in our case of diencephalic autonomic epilepsy is believed to be another proof of the diencephalic site of action of the drug.

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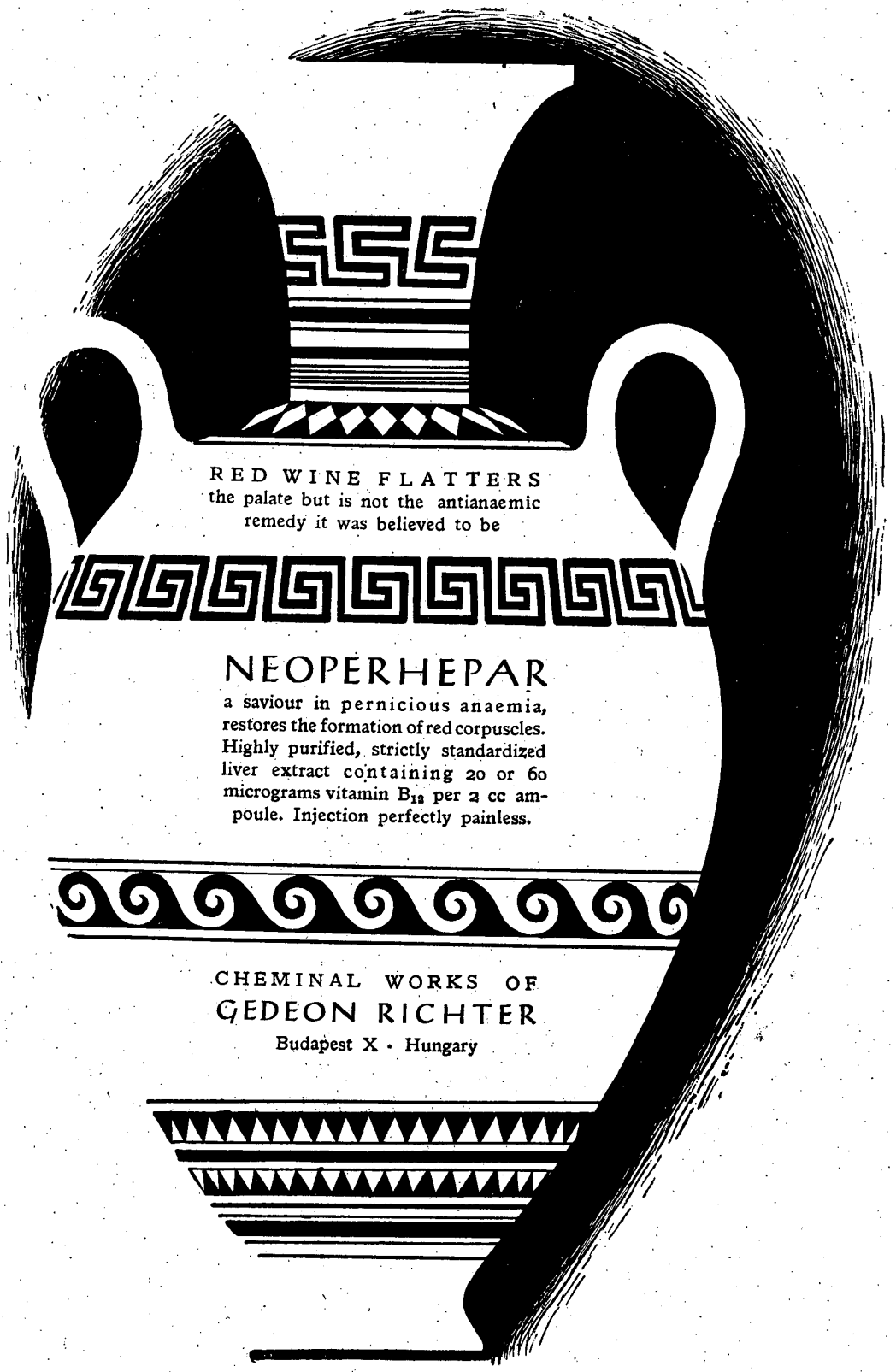


HUNGARIAN PHYSICIANS AND GARDENING

The association of physicians with gardening reaches back to the remote past. The physicians of the civilized peoples of antiquity, as Hippokrates, the "father of medicine", Dioskurides, author of a book on medicative substances, Galen, the celebrated representative of the ancient Greco-Roman school of medicine, the Roman Celsus, author of the book "De medicina", all had gardens where they grew plants to prepare medicines for their patients. In the Middle-Ages, such gardens serving medical ends were cultivated by monks engaged in healing the sick.

In Hungary, too, many monasteries grew in their gardens medicinal plants and herbs which soon found their way also into the gardens of non-ecclesiastics, commoners and nobles. Though we have no detailed description of such gardens, monastic or secular, a few records found in old deeds testify that they did in fact exist. In the year 1254, Magister Bonaventura, Provost of the Chapter of Vasvár, "Physicus Capellanus", issued a decree defining the duties of the "fratres herbacisti et rhizotomi" employed in the restored monastery-gardens. Restoration of the monastery-gardens dating from the reign of Saint Stephen until 1241 was rendered necessary by the devastations of the Tartar invasion. Some 300 years later a great many of these restored monastery-gardens and the medicinal gardens planted after their pattern fell a prey to the ravages of the Turkish conquest.

The Turks also destroyed the gardens of King Mathias in Buda* and at Visegrád. According to the testimony of contemporary records, the garden of the royal palace at Visegrád abounded in herbs of healing power and beautiful flowers; it was also adorned with an alabaster well-frame and a cupola resting on marble columns. Forty broad stairs led to the even more ornate upper court where the visitor could not only delight in the emerald-green lawn and the plenty of lovely flowers, but also rest under shady linden-trees. This garden was also mentioned in a letter written to Pope Sixtus IV by the Papal Nuncio visiting Hungary. Ha dated it "Ex Visegrado, paradiso terrestri die 25. octobris 1483". This earthly paradise was also put to ruin during the Turkish conquest.

After the "Battle of Mohács" only the gardens situated in those parts of the country which escaped Turkish rule were spared from ruin. Beside many gardens of the high nobility and of urban communities that of György Purkircher, a physician of Pozsony, enjoyed great fame. In 1556 at the University of Wittenberg Purkircher studied together with Peter Melius-Juhász, author of the "Herbarium", the first book on herbs written in Hungarian. He then studied medicine at Padova where he got into touch with János Sámboky-Sambucus, a celebrated Hungarian humanist and art-collector of the 16th century, friend and historian to the emperor; the friendship between Purkircher and Sambucus was kept up also in later years. After obtaining his doctor's diploma Purkircher went to Paris in order to improve his botanical knowledge. He returned to his native Pozsony in 1566 and practised as a physician until his death in 1578, at the age of forty-eight years.

* The old town of Buda does not extend over the entire area of three districts of the present capital, Budapest.

The highly cultured Pozsony physician made the acquaintance and became a friend of Charles de l'Écluse, whose latinized name was Clusius, the most remarkable botanist of his age. Round his house in Pozsony, Purkircher planted a garden in which he not only grew medicinal herbs but also experimented with the acclimatization of plants. He was the first to introduce into the country the American bean *(Phaseolus vulgaris)* of which he sent some seeds to Clusius. The new bean species was named by Clusius "Phaseolus Purkircheri".

The planting of a number of medico-botanical gardens followed in quick succession. The garden of the Archbishop of Esztergom, György Lippai, laid out after Purkircher's system, was renowned for its beauty. It was this garden that inspired the Jesuit monk, János Lippai, younger brother of the archbishop, to write the first original horticultural book in Hungarian under the title "Posoni kert" (Garden of Pozsony), published in 1664. Good-sized herb-gardens were planted by many physicians in North-Hungary, for instance at Lőcse by Dávid Spillenberger who in addition to herb-growing experimented also with acclimatization.

The botanical garden of the Késmárk physician Christian Augustini (Chr. Augustini ab Hortis) was one of the most notable in that age. Augustini studied medicine at Jena, Leipzig, and Wittenberg, and then became the pupil of Gaspard Bauhin, a physician and botanist at Basle. Bauhin, the last of the line of "patres botanicorum", the fathers of botanists, was the first to give a new and sound trend to botanical research. He endeavoured to draw a line between "species" and "genus" and introduced the double nomenclature.

Augustini acquired a high reputation in his native Késmárk where many people from distant places came to seek his medical advice. In the year 1631 he was summoned to Vienna by Ferdinand II who appointed him as Court Physician. He planted a botanical garden in Vienna for which he was awarded the title "ab Hortis" and raised to the rank of nobility.

Augustini invented the so-called "Carpathian" or "Hungarian" balsam which contained as ingredients the edible kernel of the cembra pine *(Pinus cembra)*, the resin of the dwarf pine, and—according to the testimony of the recently discovered contemporary prescription—the oil of the juniper *(Juniperus communis)*. It was in great demand all over Europe and R. I. Thornton, in his book "New Family Herbal", has much praise for the good effects of "Hungarian Balsam".

Among the herb-gardens of 18th century physicians the one deserving special mention is that of the Debrecen physician József Csapó, to which the book entitled "New Hungarian Herb and Flower Garden" contains several allusions. Csapó studied at Strasbourg and in Switzerland and graduated as doctor of medicine at Basle. His first medical work "Disquisitio de praesentia liquidi nervei in musculo" in Latin appeared at Strasbourg. His first book in Hungarian, "Kisgyermekek ispitálja" (Small Children's Hospital), published in 1771, deals with the well-known diseases and bodily defects of children. Over 32 years he was head-physician of the city of Debrecen and it was he who treated the consumptive son of his colleague, Mihály Csokonai-

Vitéz, the most distinguished Hungarian lyric poet before Petőfi.

A contemporary of Csapó, István Mátyus, had a medico-botanical garden at Marosvásárhely. Mátyus studied medicine at Utrecht and there published his study "Dissertatio medica theoretico-practica de melancholia universali et hypochondria" which attracted great attention. In 1757 he settled at Marosvásárhely and there wrote his book "Ó és új diaetetica" (Old and New Dietetics) in six volumes, describing various methods and the natural resources that help to preserve life and restore health, herbs, spices, vegetable plants, and fruits.

An enthusiast of gardens in those times was the Pest University professor, József Jakab Winterl. An Austrian by descent, he was appointed professor of chemistry and botanics at the medical faculty of the University of Nagyszombat founded by Péter Pázmány. Seven years later, when the university was transferred to Buda, Winterl came with it; the plants brought from Nagyszombat he tended in his own garden. These were the plants which formed the nucleus of the new botanical garden of the university when it was later transferred from Buda to Pest. The further development of the garden is associated with the name of Winterl's assistant, Pál Kitaibel. A prominent figure in Hungarian medico-botanics, physician and botanist to the core, Kitaibel was active also in other fields of natural sciences. He was the first to produce prussic (hydrocyanic) acid in its pure form, invented chloride of lime and was the first to employ it for the bleaching of textiles and wax. His most important achievement was the production of tellurium which, however, fell into oblivion for a long time.

From the middle of the 19th century medico-botanical gardens gradually lost in importance as the cultivation and gathering of medicinal herbs was taken up by agriculture. But the interest of doctors for gardening did not cease. The first Hungarian commercial gardening enterprise and nursery was installed by Ferenc Entz. A pupil of the celebrated Hartmann in Vienna, he obtained his doctor's degree there, in 1831. He took an active part in the fight against the cholera epidemic of Vienna. On his return he established himself as a medical practitioner on the Enying estate of Duke Batthyány at Mezőkomárom, but he also found time for gardening, planting a vineyard, an orchard, and a nursery. By 1847 he propagated as many as 55 kinds of apple-trees, 56 varieties of pears in addition to several types of peaches and quince. He developed a species of peach named "Duránc of Mezőkomárom". In the War of Independence of 1848—49 he filled the rank of Chief Military Surgeon. In 1850 he gave up the medical profession, settled in Pest and, with a few friends, went in for commercial gardening, laying out a garden and nursery on the precincts of the city and connecting it with a school for gardening. Appointed in 1860 as head of the school for the training of vine-dressers and gardeners on the slopes of Mount Gellért in Buda, he embarked upon extensive literary activities. He is remembered by a number of fruit specialities bearing his name, as the Entz black cherry, the Entz apricot, the Entz rosemary-apple.

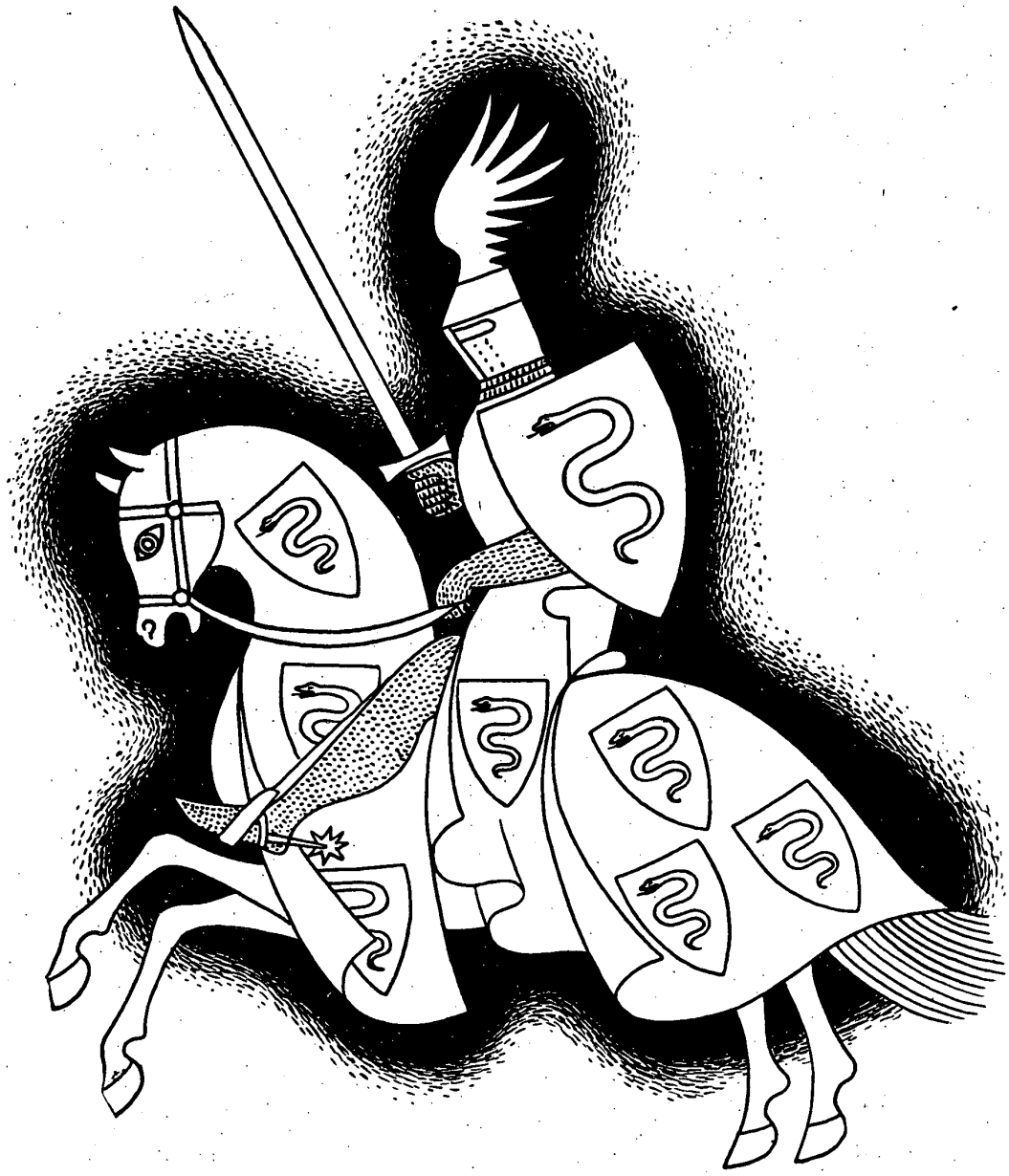
In the present century horticulture has set itself the task of plant-improvement and the development of new varieties. It is in this line that Dr. Vilmos Manninger, the prominent surgeon and professor at the University of Budapest, pursued his activities in gardening. His garden, situated in a distinguished residential suburb of Buda, was a veritable collection of various landscape-gardening elements, serving at the same time the purpose of flower improvement.

Vilmos Manninger graduated as doctor of medicine in 1898. He worked in several hospitals of the city and was finally appointed chief-surgeon of János Hospital. He wrote a number of medical works, "The History of Antiseptic and Aseptic Methods of Healing" was awarded the Vigyázó Prize by the Hungarian Academy of Sciences.

In a study on the origin of his garden he wrote: "The love of gardening I have inherited from my father. After the very exhausting daily work of his medical practice, he used to find respite in planting his garden, a place rich in beautiful pines, and later also an orchard and a vineyard. These instincts lay dormant until I reached the age of fifty. I always had so many other and more important things to do that the gardening vein was suppressed." Once the horticultural impulse asserted itself the "erudite and steady handed surgeon" produced many surprising new flowers in his garden at Buda. Thus by crossing the Chinese delphinium *(Delphinium sinensis)* with the perennial garden delphinium *(Delphinium cultorum)* he succeeded in growing various delphiniums of rare beauty and perfect form. But his results with dahlias, and particularly with primroses by developing the "Hungarian primrose", were even more spectacular. He embarked upon this task in 1932. He crossed an English garden primula, the white flowered tall primrose *(Primula elatior)* and the medicinal primrose *(Primula officinalis)* with the dwarf primrose *(Primula Juliae)*. In the following year he crossed the blue flower of the dwarf primrose and the yellow-eyed red-fringed garden primrose—itself the result of crossing—with the yellow flowered form of the tall primrose. An infinite variety of primroses were evolved in this way; he picked out those with the biggest flowers and, in 1935, crossed two specimens—one conspicuous for its red colour and yellow fringe, the other for its abundant inflorescence. This is the origin of the stem that year by year brought forth delightful novelties in "Hungaria" primulas, which were awarded a gold medal. The early death of Prof. Manninger was a sad loss to Hungarian horticulture as it cut off his experiments.

A cursory survey of the horticultural activities of Hungarian physicians over five centuries shows that by systematic cultivation of wild medicinal-herbs in gardens they laid the foundations of Hungarian botanical drug production and indirectly of the now highly developed pharmaceutical industry. Moreover, they contributed many additions to the long line of excellent Hungarian fruit varieties and enriched our flower gardens with new shapes and colours.

M. Natter-Nád



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Abstracts from Hungarian Medical Journals

Combined Colchicine-x-ray Treatment of Cancer. Duchon, J., Czigány, J., Tárcsy, G. *Orvosi Hetilap.* 96, 1311, 1955.

The damaging effect of x-ray on the tissues is known to increase in proportion to the intensification of vital processes in the tissues. An unrestrictedly growing malignant tumour is more sensitive to x-rays than is the adjacent normal tissue. In a malignant growth there are, however, cells that at the time of x-ray irradiation are in a quiescent stage; consequently the therapeutic effect of irradiation will be smaller. Colchicine is capable of delaying cellular division, arresting it in the metaphase. It has been suggested that colchicine enhances the efficacy of irradiation therapy by increasing the proportion of immature cells in a tumour. Patients with inoperable cancer have been subjected to trials. One milligramme colchicine was injected intramuscularly or subcutaneously three times a week and each injection was followed by a single dose of 200 r of x-ray irradiation. A course consisted of 20 treatments. Pain subsided after the 5th or 6th treatment and most of the patients began to put on weight. In more than 50 per cent. of cases the size of tumour and metastases decreased. No side effects were recorded, except for a tenderness experienced by some patients at the site of injection. Nevertheless, in view of the high toxicity of colchicine, authors recommend the use of this combined therapy for hospitalized patients only.

A Novel Method for the Treatment of Conditions Associated with Muscle Atrophy and Nerve Degeneration. Varga, E. *Orvosi Hetilap.* 96, 1324, 1955.

Author severed the unilateral sciatic nerve in rats and thereby produced a degeneration of the nerve. After operation, one group of the animals was given 6 mg. ATP (adenosine triphosphate, atriphos) twice a day. Two weeks after operation the gastrocnemius muscle was examined for direct and indirect excitability. This muscle and the superficial sole muscles (which have the same nerve supply) were studied for the condition of the peripheral nervous network by the author's supravital staining technique. Both the investigation of indirect excitability and the supravital staining tests have shown that the degeneration of the peripheral nervous network had been delayed by ATP treatment.

Comparative Studies of Serum Vitamin E in Normal Pregnancy and in Habitual Abortion. Tarján, R., Krámer, M., Orbán, G. *Orvosi Hetilap.* 96, 1300, 1955.

The investigations were intended to elucidate whether there was a demonstrable vitamin E deficiency in women suffering from habitual abortion. Blood samples from 247 gravidas, 86 non-pregnant women, and from 91 patients with habitual abortion were tested for vitamin E level. In normal women the mean vitamin E level was 0.99 mg.% ; in the first third of pregnancy, 0.96 mg.%, in the second third, 1.28 mg.%, and in the final third, 1.78 mg.%, while in habitual abortion the vitamin E level ranged from 1.08 to 1.57 mg.%. No deficiency in vitamin E was thus demonstrated in habitual abortion. The therapeutic results obtained by the use of vitamin E in habitual abortion are attributed to a pharmacodynamic, rather than a vitamin-like, action.

Treatment of Postoperative Duodenal Fistulae. Rigler, A. *Magy. Sebészet.* 8, 239, 1955.

Postoperative duodenal and pancreatic fistulae are known to heal very slowly. The delay in healing is due mainly to a flow through the fistula of digestive juices which exert an untoward action on the wound and the adjacent skin. Author modified Potter's method and tried to neutralize and inactivate the discharge. Through a rubber catheter of small diameter inserted into the duodenal and pancreatic fistula a 0.5% solution of hydrochloric acid diluted in physiologic saline was introduced by slow drip infusion at a rate of 6 to 8 drops per minute. By this treatment continued over three days, the healing time of the fistula has been reduced from several weeks to a few days. The procedure, with the use of a higher (2 to 3%) concentration of hydrochloric acid, has proved to be effective also in the treatment of small intestinal fistulae.

Repair of Surgical Defects in the Trachea by Homeotransplantation. Barna, L., Kerekes, P. *Magy. Sebészet.* 8, 192, 1955.

In dog experiments authors have repaired parietal and circular surgical defects in the trachea with fresh or preserved tracheal specimens, using the cartilage-preserving suture technique. In window defects the procedure has proved to produce good functional results. The correction of circular defects was followed by transformation into connective tissue and scar production resulting in narrowing of the tracheal lumen. The narrowing could be prevented by inserting an internal tube prothesis into the trachea and leaving it in place for 4 to 6 weeks after operation. The prothesis was then removed by endoscopy. The procedure has yielded satisfactory results also where the trachea was sutured circularly (without transplantation). In such cases narrowing of the tracheal lumen at the line of suture can be prevented with certainty only be the use of the tube prothesis.

Phenylbutazone (Butazolidine) for the Treatment of Thrombophlebitis. Kós, R., Votin, J., Dániel, F. *Orvosi Hetilap.* 96, 1170, 1955.

Authors have treated 30 patients with thrombophlebitis with phenylbutazone (butazolidine) preparations and obtained excellent results. They gave one ampoule on each of the first two days, followed by one ampoule every other day. Pain subsided within 12 hours, the patients became afebrile in 24 hours. Redness of skin, oedema, tenderness usually disappeared completely in 72 to 96 hours, having considerably subsided as early as 24 to 48 hours. The effectiveness of treatment is attributed to a favourable combined action of the butazolidine preparations. The central analgesic action of the drug is supported by the peripheral antiphlogistic and antihistaminic action as well as by the vasodilating action demonstrated also in animal experiments.

Paperelectrophoretic Studies of Serum from Patients with Down's Disease. Horváth, L., Göllesz, V., Csabay, L., Horvay, J. *Orvosi Hetilap.* 96, 1166, 1955.

Sera from 25 mongoloid idiots (Down's disease) have been examined by electrophoresis. It has been shown that in serum from such patients the mean value of gamma globulin was 25.9%, that of albumin 51.1%. The patient with Down's disease is known to be highly susceptible to infections; since the immune bodies are bound to gamma globulin, the above finding conflicts with clinical observation.

Recovery in a Case of Darier-Roussy Sarcoid on Treatment with Isonicid. V. Farkas, L., Zimányi, I. *Orvosi Hetilap.* 96, 721, 1955.

As long as 48 years ago, Darier and Roussy claimed that the condition they described was due to tuberculous infection. Subsequently, a number of authors nevertheless failed to distinguish the condition from the other reticuloendothelioses and granulomatoses of unknown etiology. The condition was most often identified with the disease of Besnier-Boeck-Schaumann, although its tuberculous

origin could not be confirmed. Authors diagnosed the cutaneous infiltrations present for a year in a girl aged 10 years as the manifestations of a Darier-Roussy sarcoid. Isonicid (isonicotinic acid hydrazide) was given in doses of 3×2 tablets a day for four weeks, which resulted in clinical recovery. The course was repeated and by the end of the second four weeks the patient was also histologically cured. The total dose administered was 8400 mg. During treatment the patient gained 4½ kg. in weight. Histological findings in chronological order : (1) A biopsy specimen from a typical infiltration, prior to treatment: normal epidermis and corium. Below the corium most of the adipose tissue in the subcutis is occupied by lymphocytes and epitheloid cell granulation tissue, in which large areas of necrobiosis are visible. (2) After four weeks of treatment: the epidermis is thinned, the papillar layer is smooth, the connective tissue fibres of the corium run parallel. Around the dilated vessels round cell infiltration is seen, at the cutis-subcutis junction epitheloid cell accumulation with a giant cell of the Langhans type in its centre. (3) After eight weeks of treatment: thin epidermis, connective tissue fibres running parallel. In the connective tissue of the subcutis a few lymphocytes are visible.

On Cornea Transplantations. Kettesy, A. *Orvosi Hetilap.* 96, 1093, 1955.

At the Clinic of Ophthalmology, Debrecen, cornea transplantation has become a routine operation. The total number of cornea transplantations performed during the past 18 months was 142. Of these, 41 are in the stage of final evaluation. Of the latter, 16 improved, i. e. the efficiency of the operation is 39 per cent. The corneae were obtained from cadavers. The smaller discs (those 3 to 5 mm. in diameter) were not sutured, while the larger ones were sutured with an atraumatic thread prepared by the author from the tail tendon of white rats. The non-sutured discs were held in place by covering with rabbit cornea. The freshly obtained cornea was bathed in an antibiotic mixture consisting of primycin and penicillinic acid for ten minutes, submerged for three minutes in 1 per cent. formaldehyde and washed in physiologic saline. The rabbit cornea was sutured on the recipient eye prior to cutting out the disc, but the suture was knotted only when the latter was in place. Thus the disc is covered and kept in place evenly and without pressure by the rabbit cornea. None of the discs was lost, all healed ; it was only a greying of the disc that presented a problem. The results improved when 14 days following operation cortisone (in the form of eye drops and subconjunctival injection) was started and continued for a long time.

Oxytetracycline Therapy for Thromboembolism. Horányi, M., Ferkó, S. *Orvosi Hetilap.* 96, 1050, 1955.

In 7 cases of grave, septic thrombosis and thromboembolism authors used oxytetracycline with good success. The effect, as compared to that of the antibiotics given prior to oxytetracycline, was remarkably good, although the formerly administered antibiotics combined favourably to produce a broad-spectrum action. In view of this evidence it is assumed that oxytetracycline exerts an action also on the blood coagulation system, but authors have so far failed to prove this either in vivo or in vitro.

Experience with the Mesobiliviolin Reaction. Magyar, I., Mrs. Tóth, I. *Orvosi Hetilap.* 96, 1016, 1955.

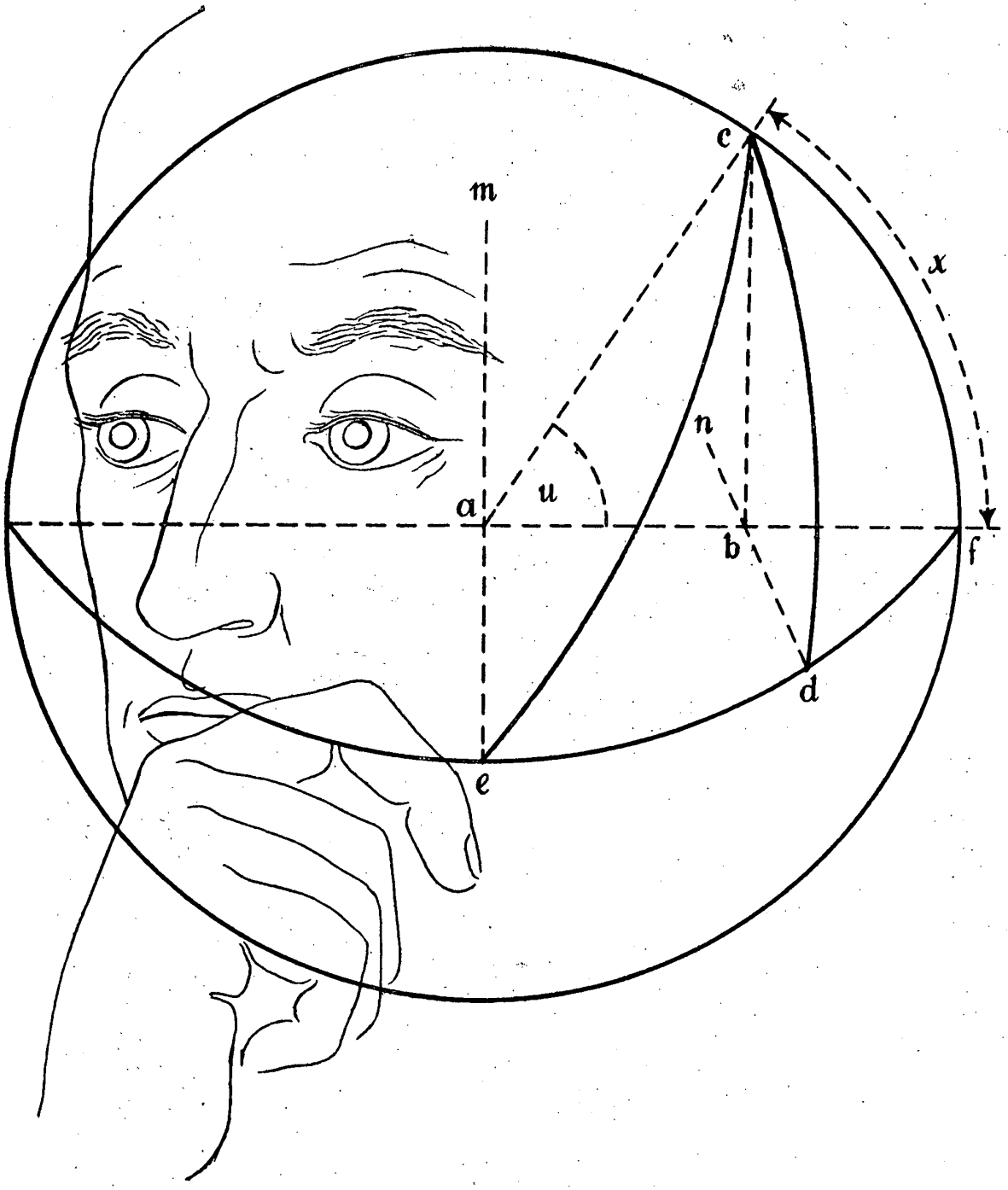
Authors report on 115 patients tested for urobilinoid excretion by the Baumgärtel method. In acute and in chronic hepatitis urobilinogen was found ; in a few cases, stercobilinogen was demonstrated as the sign of posthepatitic haemolysis. In cases of hepatic congestion stercobilinogenuria was found, which was interpreted as confirmatory of the haemolytic origin of icterus associated with hepatic congestion. In haemolytic jaundice, in pernicious anemia stercobilinogen is to be found in the urine, while in occlusion jaundice, hyperthyrosis, and febrile conditions it contains urobilinogen. The investigations have shown that the Baumgärtel mesobiliviolin reaction may be used to advantage in clinical practice for the demonstration of progress in recovery from jaundice, for the differential diagnosis of recurrent jaundice, and the recognition of haemolysis. In a certain proportion of the urine samples, both urobilinogen and stercobilinogen were demonstrable. By diluting the urine according to the procedure developed by the authors it can be shown which of these substances preponderates.

Transplantation of Deep-freeze Stored Sterile Amnion for the Prevention of Re-Adhesion of Adhesions Producing Ileus. Kubányi, E. *Orvosi Hetilap.* 96, 1382, 1955.

Numerous attempts have been made to prevent readhesion in patients operated for adhesions. The leading principle in such procedures is to make the intestinal portions slippery and to ensure natural bowel motion. In earlier histological studies it has been shown by the author that, histologically, the human peritoneum and amnion are closely related. The report discusses 7 transplantations of sterile amnion obtained by caesarean section (in 3 cases deep-freeze stored). The operation is recommended for cases where laparatomy has been performed several times and there may be a tendency to develop ileus again unless the intestinal portions deprived of their peritoneal coat are prevented from forming new adhesions.

The Effect on Secondary Wound Healing and Epithelisation of Blood Introduced into the Wound. Ladányi, J., Pongrácz, E. *Orvosi Hetilap.* 96, 1388, 1955.

Trials have been in progress over more than four years at the Second Clinic of Surgery, Debrecen, to introduce blood into wounds as treatment of poorly healing varicose and trophic ulcers, major defects due to trauma, and skin defects caused by the removal of malignant growths. When the wound is bandaged, a blood cake prepared with penicillin is placed on the wound. The blood, obtained either from the patient's vein or from a donor of the same blood group, is transferred to a gauze flap soaked in 20,000 to 40,000 U. of penicillin in a Petri dish and allowed to clot there. This cake is held on the wound by a mastisol bandage and changed every other day. In 21 out of 23 cases of crural ulcer wound healing time was remarkably reduced by this treatment. The blood cake method has been employed in 22 cases to promote the filling of soft tissue defects ; healing was characterized by the development of good scars not fixed to the base. Such scars are of exceptional importance in the healing of periarticular wounds. The procedure has proved to be effective also in the therapy of areas previously treated with x-ray irradiations.



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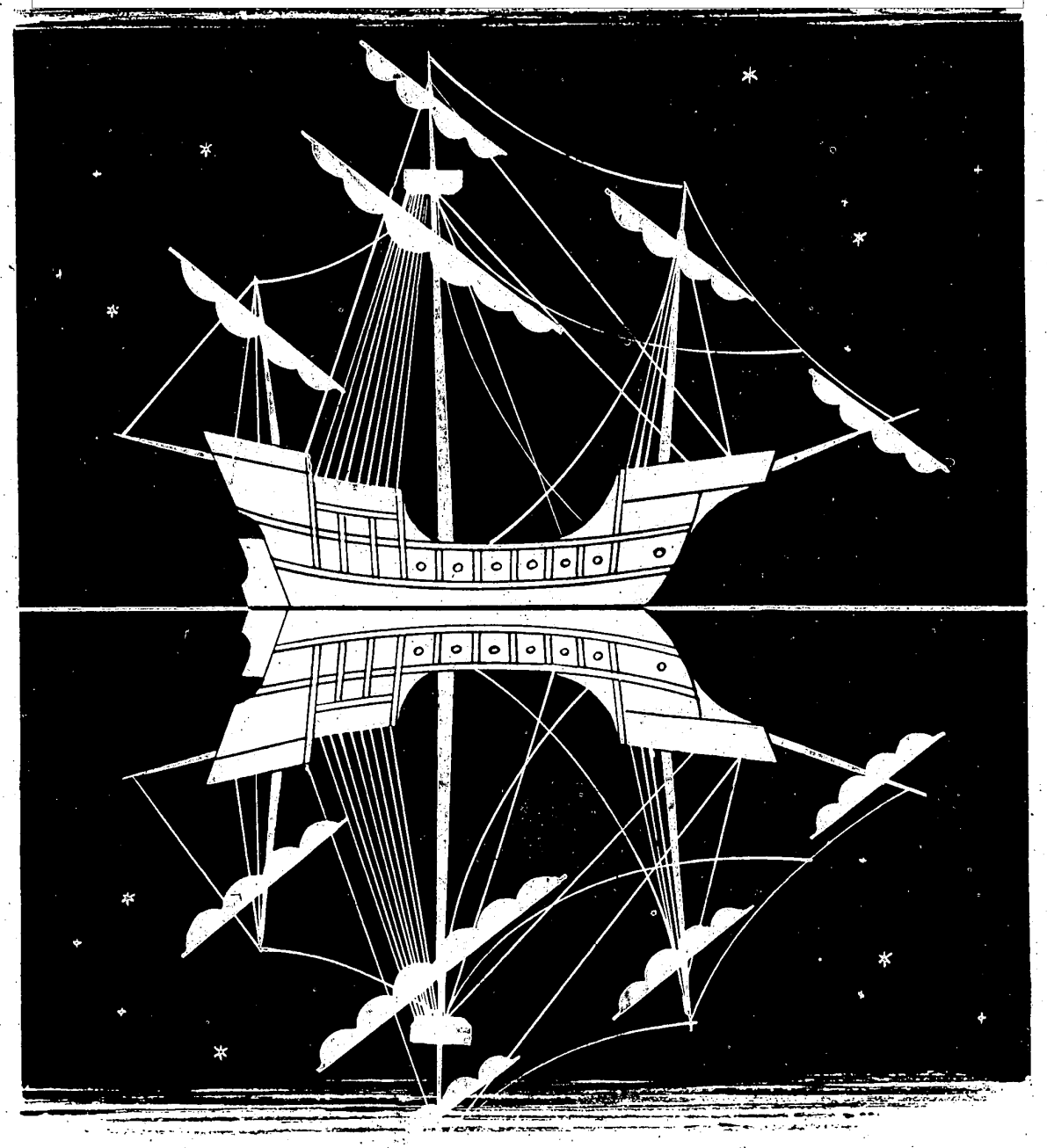

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